INTEGRATED NUTRITIONAL AND FUNCTIONAL ASSESSMENT IN BARIATRIC AND METABOLIC SURGERY

MARIEKE SMELT

Propositions

1. Vitamin deficiencies after Sleeve Gastrectomy have been underestimated for years. (this thesis)

2. Improving patient adherence to multivitamin supplement intake is the cornerstone in reducing vitamin deficiencies after bariatric surgery. (this thesis)

3. The awareness of refeeding syndrome in malnourished patients as a postsurgical complication should be raised. (S. Chiappetta)

4. The abdominal wall is frequently overlooked as a potential source of chronic abdominal pain. (M.R. Scheltinga)

5. Task reallocation in healthcare or shifting tasks from doctors to physician assistants or nurse practitioners have shown promising results with regard to quality and continuity of healthcare. (H.G. Kreeftenberg)

6. Social media use is related to various aspects of wellbeing in adolescents such as poorer sleep quality, lower self-esteem and higher levels of anxiety and depression. (H.C. Woods)

Propositions belonging to the thesis, entitled

Integrated nutritional and functional assessment in bariatric and metabolic surgery

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INTEGRATED NUTRITIONAL AND FUNCTIONAL ASSESSMENT IN BARIATRIC AND METABOLIC SURGERY

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THESIS

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Table of contents

CHAPTER 1

General introduction

1

General introduction

The World Health Organization (WHO) has declared obesity as one of the most serious public health issues since worldwide obesity has nearly tripled since 1975 (1). In 2016, more than 1.9 billion adults were overweight. Of these, 650 million were obese, accounting for 13% of the overall population worldwide (2). Overweight and obesity is defined as abnormal or excessive fat accumulation. It is associated with a higher risk of type 2 diabetes mellitus, cardiovascular diseases, obstructive sleep apnea syndrome, musculoskeletal disorders, and a higher risk of developing psychological problems and certain types of cancers (2-4). Body mass index (BMI) is the most commonly used scale to classify overweight and obesity (4):

- BMI < 18.5 kg/m^2: underweight
- BMI 18.5 – 24.9 kg/m^2: normal weight
- BMI 25.0 – 29.9 kg/m^2: overweight
- BMI 30.0 – 34.9 kg/m^2: obesity (class 1)
- BMI 35.0 – 39.9 kg/m^2: severe obesity (class 2)
- BMI > 40.0 kg/m^2: morbid obesity (class 3)

Treatment of obesity

The treatment of obesity is divided into non-surgical and surgical treatment. The cornerstone of all obesity treatment programs is lifestyle change, alongside regulation of energy intake, improvement of physical activity, reducing fat mass and increasing lean body mass (5). Obesity is a chronic disease that requires persistent management. It is challenging for patients to maintain behavioral changes, which is the most crucial factor to uphold health benefits (6). The Swedish Obesity Study was the first prospective controlled trial comparing effects of surgical and non-surgical obesity treatment for up to 20 years (7). This study is a landmark study in the field of obesity treatment and bariatric surgery. Overall, non-surgical obesity treatment did not lead to significant weight loss in the long-term. Bariatric and metabolic surgery is recognized as a highly effective therapy for obesity with significant weight loss and reduction of overall mortality and comorbidities (7-10). Preoperative patient selection is implemented in accordance with the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) criteria: age 18-65 years, class 3 obesity, class 2 obesity with at least one of the obesity related co-morbidities (such as hypertension, dyslipidemia, cardiorespiratory problems, diabetes mellitus, sleep apnea or severe joint disease), reasonable attempts at other weight loss techniques, capacity to understand the risks and commitment associated with the surgery and at last, no drug dependency problems (4).

Obesity center Eindhoven

The obesity center of the Catharina Hospital Eindhoven (CZE) is a high-volume center where 1000 procedures are performed yearly. Primary Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), one anastomosis gastric bypass (OAGB) and secondary revisions from adjustable gastric banding (AGB), vertical banded gastroplasty (VBG) or SG to RYGB, OAGB or single anastomosis duodenal ileal bypass (SADI) are performed laparoscopically. The preoperative screening and postoperative outpatient clinical care are performed by a multidisciplinary team (Table 1 and 2). After five years, lifelong annual follow-up is delegated to the general practitioner (5).

Table 1: regular preoperative screening and treatment process

MT	Presentation	IC	MM	Decision MT	IC	Presentation	CG
Surgeon	G			1. No approval 2. Preoperative counselling programme: dietician and/or psychologist 3. Approval	X		
Bariatric nurse	G	X	X			G	X
Dietician	G	X	X			G	
Psychologist	G	X	X			G	
Physiotherapist	G	X	X				

CG: commitment group, G: group, IC: individual consultation, MM: multidisciplinary meeting, MT: multidisciplinary team

Table 2: timetable of postoperative treatment process

Healthcare professional	1m	3m	6m	12m	18m	24m	36m	48m	60m
Surgeon		X				X			
Dietician	X	X	X	X					
Bariatric nurse	X		G		G		X		
Physiotherapist		X	X						
Psychologist				G	G	G			
PA or NP				X				X	X
Additional analysis	**1m**	**3m**	**6m**	**12m**	**18m**	**24m**	**36m**	**48m**	**60m**
Weight / BMI	X	X	X	X	X	X	X	X	X
Obesity related co-morbidities			X	X		X	X	X	X
Laboratory checks				X		X	X	X	X
Physical tests		X	X						
Quality of life	X			X		X	X	X	X

BMI: body mass index, m: months, X: individual control, G: group session, NP: nurse practitioner, PA: physician assistant

Nutritional management

The prevalence of micronutrient deficiencies in patients with overweight and obesity is high. The most common vitamin deficiencies are as follows: vitamin B1 (29%), vitamin B12 (2-18%), folic acid (54%), iron (45%), vitamin A (14%) and vitamin D (90%) (11).

Bariatric surgery can result in several vitamin deficiencies and can exacerbate pre-existing deficiencies. Postoperative patients are prone to develop nutritional deficiencies. This is due to malabsorption by anatomical alterations of the gastro-intestinal tract, which affects the digestive pathway and causes changes in the microbiome and hormonal balance (12). Furthermore, patients can only eat small amounts because the volume of the stomach or the pouch is significantly reduced (13). Therefore, the emphasis is on the intake of macronutrients, of which proteins are most important, because insufficient protein intake leads to a decrease in muscle mass (14-16). The nutritional diet after bariatric surgery often contains insufficient amounts of vitamins (17). Vitamin deficiencies affect the majority of the patients and can be considered as the most common problem after bariatric surgery (13). Most reported vitamin deficiencies postoperatively are vitamin D, vitamin B12, vitamin B1, folic acid and iron (11, 18, 19). These deficiencies can lead to serious neurological, hematological and musculoskeletal complications (20). To optimize long-term health after bariatric surgery, it is important to screen for and recognize symptoms of a deficiency and prescribe lifelong use of a multivitamin supplement (MVS) (20, 21). In most bariatric centers in the Netherlands, specialized weight loss surgery (WLS) MVS are advised. These specialized formulas are tailored to the specific nutritional needs after bariatric surgery. If patients prefer not to use this specialized formulas, a regular MVS is advised with 100% or 200% of the recommended daily intake (for SG and RYGB, respectively) (21). In this thesis the specialized WLS MVS are compared with regular MVS. In addition to this, different vitamin B12 and D supplementation regimens will also be analyzed.

Vitamin B12

Vitamin B12, also known as cobalamin, is a water-soluble vitamin and only found in animal products such as dairy, dairy products, meat, liver, eggs and fish. Vitamin B12 is absorbed by active and passive absorption. Active absorption occurs in the ileum when vitamin B12 is bound to intrinsic factor (IF). Passive absorption is independent of IF and occurs by diffusion along the entire length of the gastro-intestinal tract. Vitamin B12 is necessary for the production of red blood cells and the proper functioning of the nervous system (22, 23, 24). An untreated B12 deficiency can result in bone marrow failure, demyelination of the brain, peripheral nerves, optic nerve and spinal posterior and lateral columns (25-27). Adequate detection and treatment of vitamin B12 deficiencies is vital to prevent for these complications. However, there is no consensus on the best way to detect vitamin B12 deficiencies. In the past, serum vitamin B12 was used and many vitamin B12 deficiencies went unrecognized due to the high failure rate of this biomarker in 22 to 35% of the measurements (27, 28). Currently, we use combined biomarkers serum vitamin B12 and methyl malonic acid (MMA) in our obesity center. MMA is the most sensitive biomarker of the vitamin B12 status and using these combined biomarkers is therefore the most effective way to identify a deficiency (21, 23, 27, 29-32).

However, adding serum MMA greatly affects the laboratory costs, because MMA is a more expensive biomarker than vitamin B12 (€85.39 vs. €6.20 respectively) (33). Therefore, it is necessary to document if patients benefit from testing with combined biomarkers.

Furthermore, there is no consensus on the most optimal treatment regimen in the case of vitamin B12 deficiencies. In particular, the frequency and duration of intramuscular hydroxocobalamin injections in deficiency treatment should be further investigated (11, 21).

Vitamin D

Vitamin D is a fat-soluble vitamin with several bioactive variants. Ergocalciferol (vitamin D_2) is produced in certain mushrooms and fungi under the influence of sunlight. Cholecalciferol (vitamin D_3) is found in foods of animal origin (meat, liver, eggs, dairy products, and fatty fish such as herring, salmon, and mackerel). Cholecalciferol is also an added ingredient to margarine and baking products. The human body can produce vitamin D_3 in exposure of sunlight (34). Vitamin D is absorbed in the distal jejunum and ileum and afterwards converted to Calcidiol (25-hydroxyvitamin D) in the liver. This form is suitable to identify a biochemical deficiency (21, 34-37). Afterwards, Calcidiol is converted to Calcitriol (1,25-dihydroxyvitamin D) in the kidneys. Calcitriol circulates in the circulatory blood system but is not suitable for detecting a vitamin D deficiency (34). Calcitriol stimulates intestinal calcium absorption, inhibits the release parathyroid hormone (PTH) with less mobilization of calcium from bones and decreased renal calcium and phosphate excretion.
A lack of vitamin D is caused by a low oral vitamin D intake and insufficient exposure to sunlight. The prevalence of vitamin D deficiencies is reported to be as high as 90% in patients with obesity. After bariatric surgery, there is a wide variation in the incidence of vitamin D deficiencies from 20-51% in various studies (18, 19, 21, 35) and up to 100% described in the international guidelines (11, 35). A vitamin D deficiency can cause hypocalcemia, osteomalacia and muscle weakness (34, 35). Secondary hyperparathyroidism can also contribute to decreasing vitamin D, which can cause loss of bone mass and osteoporosis (34). Heaney et al. and Muskiet et al. reported that serum PTH did not further decrease statistically by serum 25-hydroxyvitamin D values of approximately 80 nmol/L (38, 39). It appears that 400 international units (IU) vitamin D contained in the standard multivitamin supplementation (MVS) after bariatric surgery may not provide adequate protection against an increase in PTH and bone resorption (21, 40, 41). Therefore, additional cholecalciferol supplementation regimens were prescribed at our center next to daily MVS use. The biochemical effect of these regimens was investigated in this thesis.

Patient adherence

Bariatric patients must adhere to many lifestyle changes and life-long use of MVS after surgery. Many patients stop taking MVS or become less consistent with MVS intake over time, despite proven effectiveness and recommendations from international guidelines. This could play an important role in the development of vitamin deficiencies (11, 17, 42-44). Insight into contributing factors is necessary in order to improve patient adherence to MVS use. In this thesis we analyzed which potential factors influence MVS use in bariatric patients.

Aim and outline of this thesis

The aim of this thesis was to optimize all aspects regarding vitamin deficiencies after bariatric and metabolic surgery. Prevention, detection and treatment of vitamin deficiencies represent cornerstones of long-term nutritional surveillance. The focus of the studies in this thesis was on vitamin B12 and vitamin D. Specific evaluation was performed on the differences between WLS MVS and regular MVS. Furthermore, we tried to obtain improved understanding of the factors influencing patient adherence to MVS intake. The goal of this thesis is addressing several important issues encountered in daily clinical practice:

- Can we reduce the percentage of vitamin deficiencies by using the specialized WLS MVS?
- How can we improve the detection of vitamin B12 deficiencies after bariatric surgery?
- What is the biochemical effect of different vitamin B12 supplementation regimens in deficient patients?
- Does vitamin B12 treatment in patients with serum vitamin B12 between 140 and 200 pmol/L result in biochemical and clinical improvement?
- What is the effect of different cholecalciferol supplementation regimens on biochemical and physical fitness outcomes?
- Which factors affect patient adherence to MVS intake?

This thesis will be split into two parts. Part one reports on vitamin deficiencies, nutritional and functional assessments in patients after bariatric and metabolic surgery. The second part reports on patient adherence and integrated health assessment after bariatric and metabolic surgery.

Part I: Nutritional and functional assessment in bariatric and metabolic surgery

In **Chapter 2** we described the effectiveness of the specialized WLS MVS for SG patients compared to regular MVS for up to 4 years. The effect on serum vitamin levels and percentage of de novo deficiencies was described. **Chapter 3** provides a systematic review regarding the effect of different vitamin B12 supplementation regimens to treat postoperative deficiencies. In **Chapter 4**, we aim to assess whether intramuscular hydroxocobalamin injections result in biochemical and clinical improvements in patients with serum vitamin B12 between 140 and 200 pmol/L. In **Chapter 5**, we aimed to optimize the dose of the intramuscular hydroxocobalamin injection regimen. The effect of three different supplementation regimens on serum vitamin B12 and the prevalence of vitamin B12 deficiencies was analyzed.

In **Chapter 6**, the effect of low serum 25-hydroxyvitamin D, high dose cholecalciferol supplementation and protein intake on physical fitness (handgrip strength and shuttle walk run test) is described. In **Chapter 7**, the variations of different cholecalciferol supplementation regimens and its influence on serum 25-hydroxyvitamin D, calcium and parathyroid hormone after bariatric surgery were analyzed.

Part II: Adherence to multivitamin supplementation after bariatric and metabolic surgery

Chapter 8 provides a narrative review to elucidate the potential barriers in patient adherence to MVS intake after bariatric surgery. We sought knowledge from other patient populations, using chronic medication or supplementation to find potential factors that could improve patient adherence in the obese population. **Chapter 9** is a cross-sectional multicenter survey study to analyze which potential barriers influence patient adherence to MVS intake. Results of an anonymous digital 42-item survey about patient adherence from patients' perspective were described.

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PART I

Nutritional and functional assessment in bariatric and metabolic surgery

CHAPTER 2

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 weight loss surgery (WLS) bariatric multivitamin (Optimum) for SG patients on deficiencies compared to a regular multivitamin supplement (MVS) for up to four 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-user group. The use of WLS MVS resulted in higher serum vitamin B1, vitamin D, vitamin B12, folic acid and ferritin. In favor of the WLS users group significant less de novo deficiencies were found of vitamin B1 (two years), folic acid (one and two years) and vitamin B12 (at one year). In contrary, anemia, iron deficiencies and hypervitaminosis B6 were diagnosed more often in the WLS users group. The total number of de novo deficiencies was significantly reduced during the whole study for all WLS Optimum users.

Conclusion

Vitamin deficiencies are common and postoperative nutritional management after SG is underestimated. The use of WLS MVS resulted in higher mean serum concentrations and less deficiencies of vitamin B1, folic acid and B12. This study shows that SG patients benefit from WLS MVS, but adjustments are required for iron and vitamin B6 content.

Introduction

The World Health Organization has declared obesity as one of the most serious public health issues. A raised body mass index increases the risk of comorbid conditions such as cardiovascular diseases, which were the leading cause of death in 2012, diabetes mellitus (DM), musculoskeletal disorders and some types of cancers. In 2016, almost two billion adults, 18 years and older, 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 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 a regular multivitamin supplement (MVS), especially when deficits are present before BS. Regular MVS 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 three 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 one year resulted in significantly less deficiencies of ferritin, vitamin B12 and folic acid compared to 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 B12 (14 – 20%), vitamin D (67 – 89%), and an elevated parathyroid hormone (PTH) (15 – 60%). 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 WLS Optimum in a normal clinical setting for SG patients on deficiencies compared to a regular MVS for up to four years. We hypothesize that specialized WLS MVS lead to less vitamin and mineral deficiencies compared to 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 six-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, serum creatinine > 150 mmol/L or liver enzymes > 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 three months and Dalteparin (5000 units/day) for four weeks. All patients start with WLS Optimum once a day, CalcichewD_3 (1000mg calcium carbonate/800IU cholecalciferol) once a day and 50,000 international units (IU) of cholecalciferol once a month. 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). All patients followed a strict postoperative five-year follow-up programme consisting of four visits to the outpatient clinic during the first postoperative year (at six weeks, three months, six months and one year) and twice a year for the next four years. Two groups were compared in this analysis, the users (WLS Optimum) and the non-users (regular MVS).

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 orgastric 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 four to six 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.

Table 1: Composition of regular MVS and WLS Optimum

		Regular MVS		WLS Optimum	
Ingredients	**Value**	**Dosage**	**RDI (%)**	**Dosage**	**RDI (%)**
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 B1	mg	1.1	100	2	182
Vitamin B2	mg	1.4	100	2	143
Vitamin B3	mg	16	100	25	156
Vitamin B5	mg	6	100	9	150
Vitamin B6	mg	1.4	100	2	143
Vitamin B8	µg	50	100	150	300
Vitamin B12	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, RDI: recommended daily intake, WLS: weight loss surgery, mg: milligram, µg: microgram

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 six and twelve months after surgery and annually until the fifth postoperative year. Deficiencies that were found either preoperatively or postoperatively were supplemented according to a standard protocol (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 Repice® reagents. Vitamin B_1 (thiamin pyrophosphate) and vitamin B_6 (pyridoxal-5-phosphate) were determined in EDTA-whole blood with chromosystems® 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®).

Table 2: Normal serum levels and supplementation regimens

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 B1 (nmol/L)	> 90.0	50 mg thiamine daily for 3 months
Vitamin B6 (nmol/L)	35.1 – 110.0	NA
Vitamin B12 (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	50,000IU Cholecalciferol 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

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 *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 was used to analyze the effect of both supplements on serum concentrations. Gender and age groups of ≤ 35 years, 36-59 years, ≥ 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 in this 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-users group and 679 patients in the non-users group. Baseline characteristics of all included patients were described in Table 3.

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/m²)	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, GERD: gastroesophageal reflux disease, OSAS: obstructive sleep apnea syndrome

Preoperative, 70% versus 76% of patients had one or more deficiencies respectively in the users and non-user group (*p* = 0.021). Preoperative, 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 B6 (*p* = 0.042). There was a significant difference in the prevalence in DM type 2, with a higher percentage in the user group (22% vs 17% *p* = 0.045). Also, more patients suffered from gastro-esophageal reflux disease in the user group (22% vs 17%, *p* = 0.045).

As expected, many patients were lost during follow-up. Percentage loss of follow-up was 2.4% (6 months), 15.8% (12 and 24 months), 73.5% (36 months) and 86.3% (48 months) (Table 4). 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 B1 (6 months, 1 and 3 years), vitamin B12 (6 months and 1 year) and vitamin D (6 months and 1 year). Anemia was less prevalent in the non-users group and delta calcium lower after two years.

Table 5 shows the percentages of preoperative deficiencies in user and non-user group, and de novo deficiencies in the postoperative period. In favor of the WLS users group significant less de novo deficiencies were found for folic acid (1 and 2 years), vitamin B1 (year 2) and vitamin B12 (year 1). On the contrary, at 2 and 3 years, there were significantly higher percentages of de novo anemia cases and hypervitaminosis for vitamin B6 was significantly more prominent in WLS users at 1 and 2 years. The total number of deficiencies (one or more) was significantly lower for WLS users at all time intervals.

Table 4: Postoperative mean serum concentrations (±SD) and delta's for users and non-users

Serum variables	Months	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

Table 4: Continued

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 B1	**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 B6	**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
	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 ± 12.4	***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 B12	**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: methylmalonic acid

Table 5: Percentages of preoperative and de novo deficiencies (baseline: users n = 291; non-users n = 679)

Serum variables	Users preoperative deficiency N (%)	Non-users preoperative deficiency N (%)	*P*-value preoperative deficiency	Months of FU	N Users	Users de novo deficiency N (%)	N Non-users	Non-users 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

2

Table 5: Continued

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 B1	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 B6 hypo/ hyper	2 (0.7%) 43 (14.8%)	7 (1.0%) 70 (10.3%)	***0.042***	**6**	284	0/128 (45.4%)	665	5 (0.8%)/ 263 (39.9%)	0.12
				12	221	0/112 (51.1%)	591	4 (0.7%)/234 (40.1%)	***0.010***
				24	201	0/68 (45%)	275	2 (0.8%)/84 (32.2%)	***0.022***
				36	119	2 (2.3%)/43 (48.9%)	134	1 (0.8%)/43 (35.5%)	0.09
				48	79	0/37 (66.1%)	52	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 B12	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%) 11 (7.7%)	185 (73.1%) 18 (7.1%)	0.12	**6**	123	69 (56.1%)/17 (13.8%)	291	185 (63.6%)/23 (7.9%)	0.14
				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

1 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: methylmalonic acid, FU: follow-up

Table 6 shows the outcomes of the binomial logistic regression model assessing the influence of MVS on serum concentrations postoperatively. This indicates a significant influence of MVS mainly on ferritin, folic acid, vitamin B1 and hypervitaminosis vitamin B6. The total amount of deficiencies was also independently significant lower in WLS users.

Table 6: Binomial logistic regression model assessing the influence of multivitamin supplementation of serum concentrations

Postoperative time	Serum concentrations	Coefficient	Standard Error	P-value
6 months after surgery	Ferritin	-0.004	0.002	***0.035***
	Folic Acid	-0.058	0.25	***0.020***
	Vitamin B1	-0.016	0.007	***0.017***
12 months after surgery	Folic acid	-0.066	0.015	***< 0.001***
24 months after surgery	Folic Acid	-0.128	0.047	***0.007***
	Hypervitaminosis Vitamin B6	-0.036	0.014	***0.012***
	Vitamin D	0.040	0.018	***0.027***
	One or more deficiencies			***0.039***

Discussion

This study shows that many vitamin deficiencies occur after SG, regardless 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 supplementations section. However, SG is now mentioned in the updated statements since 2013 (24, 25).

Vitamin B12 and folic acid

Vitamin B12 plays a vital role in DNA synthesis and in neurologic functioning (26). A vitamin B12 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, altered mental status (20, 27, 28). Frequently, low levels of serum folic acid accompany vitamin B12 deficiency and they can cause hyper- homocysteinemia, creating a risk factor for atherosclerosis (5).

Vitamin B12 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 B12 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 B12 is a cofactor for the conversion of folic acid to its active form, low vitamin B12 might lead to folic acid deficiencies. (30) Prevalence of vitamin B12 deficiency at 2-5 years postoperatively is 4-20% after SG (19, 24). In this study, the results were similar with significantly less de novo deficiencies in de patients who used WLS MVS.

For serum cobalamin < 200 pmol/L, it is unclear whether there is a functional cobalamin deficiency and cobalamin assays to diagnose a clinical deficiency have 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, but 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, MVS providing 400 µg/g folic acid can effectively prevent the development of folic acid deficiency after RYGB. This suggests that the 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 WLS users group. The binomial logistic regression model also showed a significant influence of MVS on serum folic acid.

Iron, ferritin, hemoglobin, 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 3 to 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 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 worldwide the preferred measurement, 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 MVS use (Table

5). Based on an inventory from a different ongoing randomized study (VITAAL I study), iron concentrations of the WLS MVS were 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, results from this study confirm the need for the iron adjustment in WLS MVS.

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 serum vitamin D. 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 observed in 70% of the patients preoperatively, with a drastic decline (probably due to aggressive supplementation) to 0.5% - 7.0% in the four years after SG. De novo deficiencies for vitamin D were in total low because of the large number of preoperative deficiencies. This most obviously led to underpowering and find any significance percentage wise.

Vitamin B1

Although rare, Beriberi is caused by a thiamin deficiency that can affect various organ systems, including the heart, gastro-intestinal 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 develop 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 serum vitamin

B1 concentrations were present in 5.5% one year after SG in the study by Van Rutte and colleagues (5). In this study, vitamin B1 deficiencies were observed in 3.6% preoperatively and postoperatively varying between 0.5% after 6 months to 6% after 2 years. The WLS MVS 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 B1 levels. A calculated 2.75 mg should theoretically be sufficient in compliant and non-vomiting patients.

Vitamin B6

Excessive hypervitaminoses B6 can cause neurologic symptoms. The number of patients with hypervitaminosis B6 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 observed 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 300 mg vitamin B6 per day for the last 6 months.

Strengths and limitations

Major strengths of this study were the large population and the postoperative follow-up of 4 years. The classification of WLS users and non-users was objectively confirmed by available MVS 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. 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. 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 any MVS, which possibly influences the outcomes. The study by Navarro et al. reported a serum folic acid concentration of five-fold compared with baseline after oral intake of regular MVS (containing 1.6 mg folic acid) (37). However, this study was performed in healthy adults without obesity, co-morbidities and bariatric surgery. Therefore, folic acid could be used as a marker for compliance, but it is unclear whether this is also applies to the bariatric surgery target group. 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 MVS has adjusted the concentrations of iron (from 150% to 200% RDI), vitamin B12 (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 number of deficiencies even further. Probably due to under powering, a number of mean serum concentrations showed no significant differences between the two groups at all follow-up moments. Mean serum vitamin B12 showed only a significant difference 1 year postoperatively in favor of the WLS-user group. Mean serum 25-hydroxyvitamin 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 WLS MVS or regular MVS. Therefore, it is difficult to assess the differences in serum 25-hydroxyvitamin 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 cholecalciferol unnecessary. However, these results confirm once again the need for this adjustment of the WLS MVS. The average same amounts as supplemented in these patients (75 µg) are now in the current version of WLS MVS. The results did however show is 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 the using MVS. The patients themselves paid MVS. However, the WLS Optimum is much more expensive than regular ('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 MVS resulted in higher mean serum concentrations of ferritin, folic acid, vitamin B1, vitamin D and vitamin B12. In favor of the WLS users significant less de novo deficiencies were found of vitamin B1, folic acid and vitamin B12, but anemia, iron deficiencies and hypervitaminosis B6 were diagnosed more often among WLS users. The study showed that SG patients should not just use lifelong standard MVS but could benefit even more from the specialized WLS MVS, but adjustments are required for iron and vitamin B6 content in these supplements.

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CHAPTER 3

Different supplementation regimens to treat perioperative vitamin B12 deficiencies in bariatric surgery: A systematic review

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Abstract

Vitamin B12 dosage in multivitamin supplementation in the current literature is quite variable. There is no consensus about the optimal treatment of a vitamin B12 deficiency. A systematic literature search on different supplementation regimens to treat perioperative vitamin B12 deficiencies in bariatric surgery was performed. The methodological quality of 10 included studies was rated using the Newcastle Ottawa scale and ranged from moderate to good. The agreement between the reviewers was assessed with a Cohen's kappa (0.69). The current literature suggests that 350 µg oral vitamin B12 is the appropriate dose to correct low serum vitamin B12 concentrations in many patients. Further research must focus on a better diagnosis of a vitamin B12 deficiency, the optimal dose of vitamin B12 supplementation and the clinical relevance next to biochemical data.

Introduction

Vitamin B12 deficiencies are common after bariatric surgery. Schilling et al. estimated the prevalence of vitamin B12 deficiency to be 12-33% (1).Other researchers have suggested a much greater prevalence of vitamin B12 deficiency in up to 75% of postoperative Roux-en-Y gastric bypass (RYGB) patients. However, most reports have shown approximately 35% of postoperative RYGB patients as vitamin B12 deficient (1-6). Experts have noted the significance of a functional/subclinical deficiency in the low-normal vitamin B12 range (defined as serum vitamin B12 between 140 and 200 pmol/l) that does not exhibit clinical evidence of deficiency. The methylmalonic acid (MMA) assay is the preferred marker of vitamin B12 status because metabolic changes often precede low serum vitamin B12 concentrations in the progression to deficiency (7, 8). The evidence for the optimal vitamin B12 supplementation regimen after bariatric surgery is lacking (9). The dose of vitamin B12 in a multivitamin supplement (MVS) in the current literature shows a wide range of variety. There is also no consensus about the optimal treatment of a vitamin B12 deficiency. This systematic review specifically focuses on vitamin B12 supplementation regimens after bariatric surgery. This review analyze the effect of regular multivitamin supplement (MVS) regimen and deficiency treatment on serum vitamin B12 concentrations, and MMA if available.

Methods

A systematic multi database literature search was conducted. The patient population of interest were all patients before or after bariatric surgery. The intervention studied was the effect of different vitamin B12 supplementation regimen compared to no supplementation. Outcome measures were serum vitamin B12 and serum MMA if available. Pubmed, Embase, Medline, and The Cochrane Library were searched from the earliest date of each database up to December 2015. The search string used for the literature search used the following keywords and was modified for each database: ([bariatric surgery OR metabolic surgery OR sleeve gastrectomy OR Roux-en-Y gastric bypass OR mini gastric bypass OR omega loop gastric bypass OR biliopancreatic diversion OR duodenal switch OR single anastomosis duodeno-ileal bypass AND vitamin B12 supplementation AND serum vitamin B12]).

Inclusion criteria

- Randomized controlled trial, prospective or retrospective cohort study
- Patients who were scheduled for bariatric surgery or patients post-bariatric
- All surgical procedures were included (laparoscopic gastric banding, vertical banded
- gastroplasty, sleeve gastrectomy, Roux-en-Y gastric bypass, omega loop bypass, duodenal switch, biliopancreatic diversion, single anastomosis duodeno-ileal bypass)
- Outcome measure of interest was serum vitamin B12, and serum MMA if available

Exclusion criteria

- Cross-sectional studies
- Studies looking at pre- and/or post bariatric patients with renal insufficiency
- Post bariatric body contouring surgery

Authors HS and SP screened and selected studies based on title and abstract, separately. After primary selection, authors (HS and SP) reviewed the full text of the selected studies and determined suitability for inclusion, based on the established selection criteria. For further eligible studies, cross-references were screened. Disagreements were solved by discussion with each other and the senior author (JS) until consensus was reached. For rating the methodological quality, The Newcastle-Ottawa Scale for non-randomized trials (NOS) was used (10). Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars. The NOS assigns up to a maximum of nine points for the least risk of bias in three domains: 1) selection of study groups (four points); 2) comparability of groups (two points), and 3) ascertainment of exposure and outcomes (three points) for case–control and cohort studies, respectively. Two authors (HS and SP) separately assessed the NOS scale of the included studies. A Cohen's kappa score was calculated to determine the level of agreement between authors HS and SP. A Cohen's kappa score < 0.20 indicates a poor agreement; 0.21 – 0.40 a fair agreement; 0.41 – 0.60 a moderate agreement; 0.61 – 0.80 a good agreement; 0.81 – 1.00 a very good agreement (11).

Measurement unit of vitamin B12 levels

All serum vitamin B12 concentrations were calculated in one general unit (pmol/L), if possible.

Results

The primary literature search produced 532 results, including 37 duplicates. After selection on title and abstract, 19 studies were found possibly relevant. Nine studies were excluded, 5 of them were conference abstracts, 2 of them were not online available, 1 study did not use MVS and 1 study consisted of a survey among bariatric surgeons. Due to heterogeneity in patient populations, small sample size of the included studies and lack of standardized reporting of outcome measures (type of supplementation regimen and dose of vitamin B12 in the prescribed supplementation), a meta-analysis was not conducted. In total 10 studies were included in this systematic review. Figure 1 outlines our search strategy.

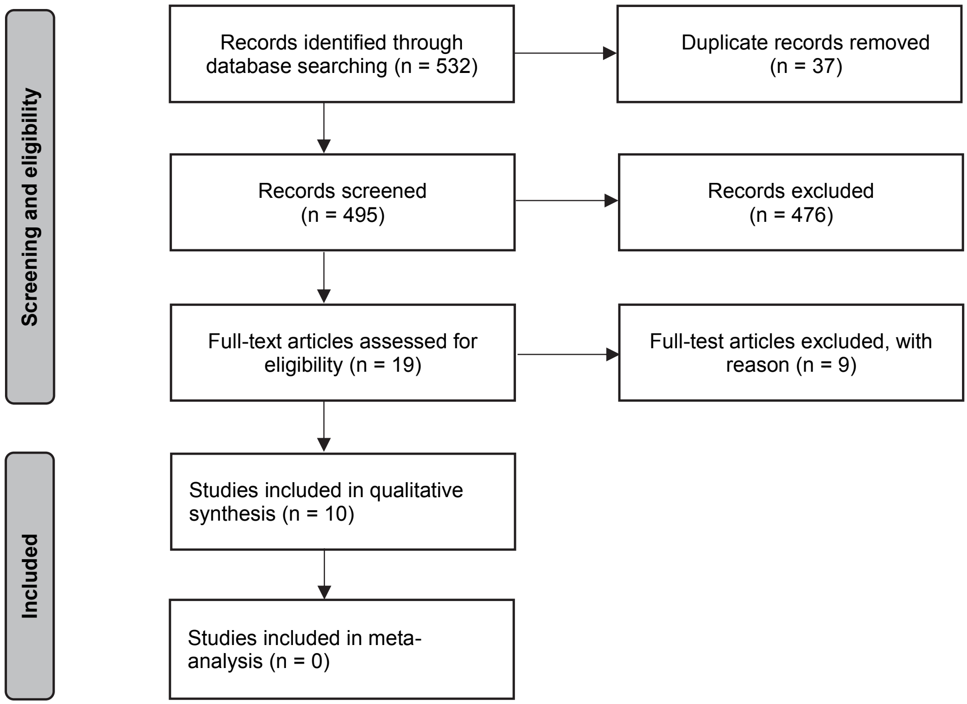

Figure 1: PRISMA flowchart

Table 1: Assessment of methodological quality using The Newcastle-Ottawa Scale for non-randomized trials (10)

Criteria	Representiveness	Selection	Ascertainment	Demonstration	Comparability	Outcome selection	Outcome follow-up	Adequacy	Total
Aasheim et al., 2012 (12)	*	-	*	*	**	*	*	*	**8**
Brolin et al., 1998 (6)	*	-	*	*	**	*	*	-	**7**
Capoccia et al., 2012 (13)	*	-	*	*	**	*	*	*	**8**
Dogan et al., 2014 (14)	*	*	*	*	**	*	*	*	**9**
Donadelli et al., 2012 (9)	*	-	*	*	**	*	*	-	**7**
Gasteyger et al., 2008 (15)	*	-	*	*	**	*	*	-	**7**
Homan et al., 2016 (16)	*	*	*	*	**	*	*	*	**9**
Moore et al., 2014 (17)	*	-	*	*	**	*	-	*	**7**
Ramos et al., 2015 (18)	*	-	*	*	**	*	*	-	**7**
Rhode et al., 1995 (19)	*	-	*	*	**	*	-	*	**7**

The methodological quality of the included studies ranged from moderate to good, indicated by the NOS scale (Table 1). A Cohen's kappa of 0.69 reflected a good agreement between authors HS and SP. Table 2 gives an overview of the results of the included studies.

Study characteristics

Of all included studies, 1 study was a triple-blind randomized controlled trial (14), 4 studies were prospective cohort studies (9, 12, 17, 19) and 5 studies were retrospective cohort studies (6, 13, 15, 16, 18). In total, 10 studies consisted of 1277 participants. The length of the intervention ranged from 3 months to 10 years postoperative (Table 2). In 8 studies, the dose of vitamin B12 in MVS was different (Table 2). The dose of vitamin B12 in MVS was not described in the studies of Ramos et al., (18) and Brolin et al., (6). Complaints due to a vitamin B12 deficiency were not described in all included studies.

Laboratory test outcomes

Outcomes of the laboratory tests were described in Table 3. All serum vitamin B12 concentrations were calculated in pmol/L, except the studies of Brolin et al., (6) and Ramos et al., (18) which suspectedly used other measurement units for indicating a vitamin B12 deficiency. Reference ranges of serum vitamin B12 of all studies were described in Table 2. Differences in serum vitamin B12 or percentage vitamin B12 deficiencies were not described in all included studies and were therefore only mentioned if these results were available (Table 3). Serum MMA was not mentioned in any of the studies.

Table 2: Overview of the study results of the included studies

Study	Design	N (male/ female)	I: N (age ± SD) C: N (age ± SD)	Standard supplementation (Dose of VB12)	Reference range serum VB12	Treatment of VB12 deficiency	Type of surgery	Outcome measure of interest	FU
Aasheim et al., 2012 [11]	Prospective cohort trial	50 (18/32)	I: 27 (44 ± ?) C: 23 (45 ± ?)	I: MVS (VB12 1 µg/day) + im cyanocobalamin 1000 µg/3 months C: no MV	ND	ND	I: RYGB C: no surgery	Blood tests Dietary intake	1 Y
Brolin et al., 1998 [6]	Retrospective cohort trial	348 (? / ?)	I: 348 (? ± ?)	MVS daily, dose ND	210 – 700 pg/dl	Standard MVS (dose VB12 ND) or additional VB12 supplementation (500 µg)	RYGB	Blood tests	10 Y
Capoccia et al., 2012 [13]	Retrospective cohort trial	138 (28/110)	I: 7 (36.7 ± 13.2) II: 29 (43.6 ± 10) III: 40 (44.4 ± 9.6) IV: 33 (45.1 ± 12.8) V: 29 (43.7 ± 10.8)	Month 1 till 6: MVS (VB12 2,5 µg/day) Month > 6: stop MVS, start im VB12 1000µg/ month	ND	ND	LSG	Blood tests Dietary intake	1 Y
Dogan et al., 2014 [23]	Randomized controlled trial	148 (46/104)	I: 74 (45.3 ± 10.2) C: 74 (43.4 ± 10.0)	I: WLS MVS (VB12 350 µg/day) C: regular MVS (VB12 12.5µg/day)	≤ 150 pmol/L	im hydroxocobalamin 1000 µg every 2 months for 1 year	RYGB	Blood tests	1 Y
Donadelli et al., 2012 [9]	Prospective cohort trial	58 (12/46)	I: 58 (41 ± 10)	MVS (dose VB12 12 µg/ day)	130 – 650 pmol/L	ND	RYGB	Blood tests	1 Y
Gasteyger et al., 2008 [17]	Retrospective cohort trial	137 (27/110)	I: 137 (39.9 ± 10)	Month 1 till 6: regular MVS (VB12 3 µg/day) Month > 6: no MV	133 – 675 pmol/L	oral VB12: 1 mg/ month In case of no satisfactory response: start im injections (dose ND)	RYGB	Blood tests	2 Y
Homan et al., 2016 [14]	Retrospective cohort trial	137 (42/95)	I: 45 (46 ± 12) II: 64 (44 ± 9) III: 28 (43 ± 10)	I: MVS (VB12 12.5 µg/ day) II: MVS (VB12 350 µg/ day) III: no MVS	≤ 150 pmol/L	im hydroxocobalamin 1000 µg every 2 months for 1 year	RYGB	Blood tests	1-3 Y

Table 2: Continued

Moore et al., 2014 [15]	Prospective cohort trial	22 (0/22)	I: 22 (41 ± 12)	MVS (VB12 350 µg/day) for 3 months	< 200 µg/mL	ND	LSG (n= 11) RYGB (n= 11)	Blood tests	3 M
Ramos et al., 2015 [18]	Retrospective cohort trial	137 (24/113)	I: 137 (? ± ?)	Regular MVS (VB12 dose ND)	≥ 250 mg/dl	ND	RYGB	Blood tests	4 Y
Rhode et al., 1995 [12]	Prospective cohort trial	102	I: ? (? ± ?) II: ? (? ± ?) III: ? (? ± ?) IV: ? (? ± ?)	Month 1 till 3: VB12 350 µg/day Month 4 till 6: oral crystalline in 4 different doses: I:100 µg / II:250 µg / III:350 µg / IV:600 µg Month 7 till 9: no supplement	150-600 pmol/L	ND	RYGB (n = 94) VBG (n = 8)	Blood tests	9 M

I: intervention group, C: control group, FU: follow-up, im: intramuscular, MVS: multivitamin supplement, ND: not described, RYGB: Roux-en-Y gastric bypass, LSG: laparoscopic sleeve gastrectomy, M: months, VB12: vitamin B12, VBG: vertical banded gastroplasty, WLS: weight loss surgery, Y: years.

Discussion

This systematic review highlights the current evidence on the effects of MVS or additional vitamin B12 supplementation in patients after bariatric surgery. Vitamin B12 supplementation influences the intracellular vitamin B12 content and in the optimal dosage it can prevent a vitamin B12 deficiency. However, vitamin B12 deficiencies preoperatively are not uncommon in morbidly obese people. In the study of Dogan et al., (14) a vitamin B12 deficiency was diagnosed in 6.1% of the patients and 5.2% of the patients in the study of Donadelli et al., (9) have had a vitamin B12 deficiency in the preoperative period. This is not clearly reported in the other 8 studies.

There is no consensus about the optimal dosage of vitamin B12 supplementation after bariatric surgery worldwide. ASMBS guidelines advise oral vitamin B12 supplements of 350 to 500 µg, and if necessary, intramuscular (im) injections of 1000 µg per month (20). The ACCE/TOS/ASMBS guidelines advice oral supplementation with crystalline vitamin B12 at a dosage of 1000 µg daily or more may be used to maintain normal serum vitamin B12 concentrations. Intranasal administered vitamin B12, 500 µg weekly, may also be considered. Parenteral (im or subcutaneous) vitamin B12 supplementation, 1000 µg/month to 1000-3000 µg every 6 to 12 months, is indicated if vitamin B12 sufficiency cannot be maintained using oral or intranasal routes (21).

However, definitive conclusions cannot be made after this systematic review, because of the heterogeneity of MVS or deficiency treatment with im injection regimens and timing of these im injections. Besides that, all the included studies did not describe the vitamin B12 deficient related complaints and therefore, the clinical relevance is unclear. These data are needed to examine whether biochemical benefits of vitamin B12 supplementation are correlated with clinical improvement. Besides that, surgical techniques affect the absorption of vitamin B12. Intrinsic factor (IF) is produced by the parietal cells of the stomach and IF is needed to absorb vitamin B12 in the terminal ileum. In this review, laparoscopic sleeve gastrectomy (LSG), RYGB and vertical banded gastroplasty (VBG) are discussed. LSG patients have reduced production of stomach acid and reduced availability of IF. In RYGB patients a vitamin B12 deficiency loss of IF and acid secretion in the stomach is expected. The remnant stomach and duodenum are eliminated from the digestion process as well. The VBG serve only to restrict and decrease food intake and do not interfere with the normal digestive process. In this procedure the upper stomach near the esophagus is stapled vertically to create a small pouch along the inner curve of the stomach. The outlet from the pouch to the rest of the stomach is restricted by a band.

Table 3: outcomes laboratory tests of vitamin B12

Aasheim et al., 2012 (12)	Serum VB12 increases after intervention, compared with the control group ($p < 0.02$). Of 2 patients who developed VB12 deficiency (compared with non in the control group), 1 reported not having had im injections. Serum vitamin B12 values were not mentioned.
Brolin et al., 1998 (6)	Serum VB12 values were significantly lower than mean preoperative values at 12 and 24 months after surgery. 37% of the patients had a VB12 deficiency and the incidence of VB12 deficiency after surgery was significantly greater in the revision group ($p \leq 0.004$). More than 80% of the VB12 deficiencies responded to oral supplementation (500 µg VB12). Serum vitamin B12 values were measured but not mentioned in the study.
Capoccia et al., 2012 (13)	VB12 was adequately supplemented for all the follow-up period (before surgery and 12 months after surgery, 365.8 ± 193.7 pmol/L and 360.8 ± 169.0 pmol/L, respectively). Baseline serum VB12: 317.3 ± 132.8 pmol/L, 286.0 ± 188.7 pmol/L, 376.8 ± 197.8 pmol/L, 517.3 ± 191.0 pmol/L, 258.8 ± 303.5 pmol/L, for group A, B, C, D and E respectively. Follow up results 12 months after surgery: 338.7 ± 284.4 pmol/L, 349.8 ± 193.3 pmol/L, 268.6 ± 119.0 pmol/L, 284.4 ± 154.3 pmol/L, 303.5 ± 187.0 pmol/L, for group A, B, C, D and E respectively. Percentage deficiencies were not mentioned in the study.
Dogan et al., 2014 (14)	VB12 deficiencies at baseline: 6.8% and 5.4% for standard MVS users vs. WLS Forte users. In total, 18.2% additional patients were treated with im injections at any time during the 12 months FU: 23% vs. 13.5% for standard MVS users vs. WLS Forte ($p = 0.14$). The results obtained after exclusion of these patients receiving im injections: mean serum VB12 decreased by 38.9 ± 141.3 pmol/L (standard MVS users) vs. 44.1 ± 138.8 pmol/L (WLS Forte users) ($p < 0.001$) after 12 months. Mean serum VB12 at 6 and 12 months were significantly higher in the WLS Forte users ($p < 0.05$). After 12 months, VB12 deficiency had developed in 7.9% vs. 1.6% for standard MVS users vs. WLS Forte users ($p = 0.207$).
Donadelli et al., 2012 (9)	Serum VB12 remained constant up to 3 months (331.7 ± 183.9 pmol/L) until 6 months (295.8 ± 183.0 pmol/L) and decreased after 12 months (274.9 ± 196.9 pmol/L) ($p = < 0.05$). VB12 deficiency was seen in 7% of the patients after 12 months.
Gasteyger et al., 2008 (15)	Additional VB12 supplementation was used in 10% of the patients at 3 months, 28% at 6 months, 62% at 12 months, 72% at 18 months and 80% at 24 months.
Homan et al., 2016 (16)	In the first 3 years, 16% developed a VB12 deficiency and were prescribed im injections (7.8% WLS forte users vs. 33.3% regular MVS users vs. 7.1% non-users). After exclusion of the im injection users, a significant difference in estimated mean serum VB12 was found between WLS Forte (335 ± 12 pmol/L) and regular MVS (264 ± 12 pmol/L) ($p < 0.001$). Percentage VB12 deficiencies after 36 months: 6,7% regular MVS users vs. 14.3% non-users. Combining the im injection users and the deficient patients resulted in 21.2% deficient patients: 7.8% 5 WLS Forte users vs. 40% regular MVS users vs. 21.4% non-users ($p < 0.001$).
Moore et al., 2014 (17)	High dose MVS for 3 months resulted in an increase of serum VB12 in 48% of the patients. A significant increase was seen in all patients after SG (from 356.5 ± 93.0 pmol/L to 466.4 ± 220.7 pmol/L, $p = 0.034$) and in all patients after RYGB (from 377.1 ± 129.2 pmol/L to 605.9 ± 295.2 pmol/L, $p = 0.033$).
Ramos et al., 2015 (18)	Male: Female: Preoperative: 464.0 ± 140.6 mg/dL 512.5 ± 561.5 mg/dL Postoperative: - 12 months: 373.8 ± 148.3 mg/dL 395.6 ± 247.0 mg/dL - 24 months: 317.8 ± 163.7 mg/dL 391.5 ± 212.9 mg/dL - 36 months: 401.4 ± 352.0 mg/dL 351.3 ± 177.1 mg/dL - 48 months: 354.4 ± 186.6 mg/dL 395.8 ± 220.3 mg/dL Percentage of deficiencies and p-values were not mentioned in the study.
Rhode et al., 1995 (19)	Serum VB12 values were <100 pmol/L at baseline and greater than 150 pmol/L after 6 months in 83.3% of patients who received 100 µg; 92.3% of patients who received 250 µg; 94.7% after 350 µg and 95.2% after 600 µg ($p = 0.525$).

FU: follow-up, im: intramuscular, MVS: multivitamin supplement, ND; not described, RYGB: Roux-en Y gastric bypass, SG: sleeve gastrectomy, VB12: vitamin B12, WLS: weight loss surgery.

Two interesting findings were found in the included studies. First, in 4 included studies a dose of 350 µg vitamin B12 per day was used (14, 16, 17, 19). In the study of Moore et al., (17) serum vitamin B12 of all patients were increased 3 months postoperatively. In the study of Dogan et al., (14) high dose vitamin B12 supplements results in fewer vitamin B12 deficiencies compared with regular MVS. The study of Homan et al., (16) showed that high dose vitamin B12 supplementation is more effective than a regular MVS to reduce the number of patients with vitamin B12 deficiencies. In the study of Rhode et al., (19) serum vitamin B12 concentrations were > 150 pmol/L after 6 months in 95% of the patients. Secondly, all the other studies used a MVS with vitamin B12 amounts ranging from 3 to 12 µg per day (9, 15) or unknown dose of vitamin B12 (6, 18). The studies of Brolin et al., Donadelli et al. and Gasteyger et al., showed many vitamin B12 deficiencies in the follow up (6, 9, 15). Contrary results were found in the study of Ramos et al., (18), were serum vitamin B12 concentrations are within the reference standards. However, the dose of vitamin B12 in his study was unknown.

Vitamin B12 supplementation

Dose of vitamin B12 in the MVS in all included studies, is varied from 1 µg/day to high dose supplementation with 350 to 600 µg per day. MVS with 350 µg vitamin B12 per day can maintain normal-high serum vitamin B12 concentrations in many patients (14, 16, 17, 19). The body’s storage will be depleted much faster in patients who using regular MVS consisted of a low dose of vitamin B12. Eight included studies showed persistence of deficiencies with an oral vitamin B12 dosage < 350 µg per day, even after a period of additional vitamin B12 treatment (6, 9, 12-16, 19). In one study (6) no dosage of vitamin B12 was described, in the other studies the dosage of vitamin B12 was lower than < 350 µg per day (9). In 2 included studies, im injections belong to the standard regimen in addition to the regular MVS (12, 13). The dose of im injections is equal, but the frequency of given im injections is also different (Table 2). In the study of Aasheim et al., (12) 4% of the patients developed a vitamin B12 deficiency despite the use of standard im injections beside regular MVS. In the study of Capoccia et al., (13) regular MVS were used in the first six months. Afterwards the MVS were stopped and im injections were started (1mg/month) (13). However, serum vitamin B12 decreased in many patients in both studies, which suggests that this both regimen were not optimal. If MVS with a high dose of vitamin B12 may improve serum vitamin B12 concentrations in many patients, im injections as a standard regimen is not necessary and because of this, many patients were unnecessary loaded with im injections. This seems like contradictory advice, but to determine whether im injections are necessary, improving the detection of a deficiency and clinical relevance of the different treatment regimens should be investigated first (7, 8, 22, 23).

Besides that, these data are subjectively, and it is unclear if patients take their supplements daily. Life-long compliance of daily supplement intake is hard to achieve. To measure adequate intake of MVS, one can monitor the serum concentration of highly absorbable vitamins. Some investigators have reported that low folate levels reflect non-adherence to MVS use, because the amount of supplemented folic acid properly corrects low serum folate levels (9, 14). Only two studies have looked at compliance of MVS intake and distinction in processing these data (14, 16).

Outcomes of laboratory tests

Vitamin B12 assays that are currently used to diagnose clinical vitamin B12 deficiency have a failure rate of 22-35% (7, 8, 22, 23). This failure rate may be due to the fact that 80% of the vitamin B12 in plasma is bound to the transport protein haptocorrin. This percentage is biologically unavailable and cannot be absorbed by the cells, which means that plasma vitamin B12 concentrations poorly correlate with the bioavailable intracellular vitamin B12 content (8, 24, 25). Therefore, measuring vitamin B12 is a poor predictor for a functional vitamin B12 status. In the study of Smelt et al., (8) more vitamin B12 deficiencies were found if MMA is included in the diagnostics. In this review, no included study used the additional parameter MMA. Given the high failure rate of vitamin B12 assays, many vitamin B12 deficiencies will be untreated.

Study limitations

First, the following limitations are present when evaluating the literature: 1) heterogeneous patient populations being studied, 2) non-comparable vitamin B12 from supplements being evaluated, 3) lack of many data (some studies lacked of gender, age, reference range of serum vitamin B12, actual serum vitamin B12 concentrations after intervention, lack of description of vitamin B12 dose in MVS) and 4) lack of well-designed prospective cohort and randomized controlled studies for the right use of vitamin B12 in post bariatric patients. Secondly, only biochemical data was measured and clinical relevance was not demonstrated.

Conclusion

In bariatric surgery, vitamin B12 deficiencies have a high prevalence. Unfortunately, there is no consensus about MVS and any additional vitamin B12 supplementation. The current literature suggests that at least 350 µg of oral vitamin B12 is the appropriate oral dose to correct low serum vitamin B12 concentrations in many patients. A lifelong follow-up regimen seems necessary, because a MVS with a high dose of vitamin B12 cannot prevent all deficiencies. Further research must focus on the improvement of deficiency detection with combined parameters, the most optimal dose of vitamin B12 supplementation and its clinical relevance.

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CHAPTER 4

Comparison between different intramuscular vitamin B12 supplementation regimens: a retrospective matched cohort study

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Abstract

Background

The incidence of a vitamin B12 deficiency after bariatric surgery can range from 26% to 70%. There is no consensus on optimal vitamin B12 supplementation in post bariatric patients. The objective of this study was to compare three different regimens.

Methods

In this retrospective matched cohort study, we included 63 patients with serum methylmalonic acid (MMA) ≥ 300 nmol/L. Group A (n = 21) received 6 intramuscular (im) hydroxocobalamin injections including a loading dose, group B (n = 21) received 3 im hydroxocobalamin injections without loading dose and group C (n = 21) received no im hydroxocobalamin injections.

Results

The total post-bariatric patient population consisted of 14 males (22.2%) and 49 females (77.8%) with a mean current body mass index of 30.6 ± 8.0 kg/m². There were no significant differences in serum vitamin B12 and serum MMA between the 3 groups at baseline. There was a significant difference in follow-up serum vitamin B12 of group A compared to group B ($p = 0.02$) and group A compared to group C ($p = 0.03$), both in favor of group A. In the follow-up results there is also a significant decrease in serum MMA of group A compared to group B ($p = 0.02$) and group A compared to group C ($p < 0.001$), both in favor of group A. There was also a significant difference in serum MMA in group B compared to group C ($p < 0.01$), in favor of group B. Serum MMA have been normalized below 300 nmol/L after treatment in all patients of group A. In group B, 28.6% of the patients did not improve sufficiently.

Conclusion

In this study, a shorter im hydroxocobalamin injection regimen is probably not sufficient to treat a vitamin B12 deficiency. An im hydroxocobalamin injection regimen with 6 injections recovered all vitamin B12 deficiencies biochemically. Serum MMA concentrations cannot recover spontaneously over time without treatment with im hydroxocobalamin injections.

Introduction

The incidence of a vitamin B12 deficiency after bariatric surgery can range from 26% to 70%. A vitamin B12 deficiency can occur in the relatively early stage postoperative but, most commonly, years after surgery when the large liver stores are slowly depleted (1). Vitamin B12 deficiency can cause pernicious/megaloblastic anemia, fatigue, light-headedness, numbness and paresthesia (tingling or prickly feeling) in extremities, demyelination and axonal degeneration (especially of peripheral nerves, spinal cord and cerebrum), changes in mental status ranging from mild irritability and forgetfulness to severe dementia or frank psychosis, ataxia and change in reflexes (2-10). To prevent a vitamin B12 deficiency after bariatric surgery, all patients have started to use an oral multivitamin supplement (MVS) daily from 2 weeks postoperative. In order to detect a vitamin B12 deficiency, patients are screened preoperatively and postoperatively. Multiple guidelines suggest that serum vitamin B12 below 140 pmol/L reflect a vitamin B12 deficiency and should be treated in addition to regular MVS (14-18). However, we previously have shown that functional vitamin B12 deficiencies might occur with serum vitamin B12 above 140 pmol/L (7). For this specific group of patients, no (inter)national supplementation advice or guideline is currently available. Previously these patients were not additionally treated.

Since serum methylmalonic acid (MMA) is a sensitive marker for functional vitamin B12 deficiencies, we have added the additional analysis of serum MMA in patients with serum vitamin B12 below 300 pmol/L in our bariatric center since June 2013. Nowadays, we start intramuscular (im) hydroxocobalamin injections in bariatric patients with serum MMA ≥ 300 nmol/L. In the first period, we used an injection regimen, which consisted of 6 im injections including a loading dose. According to current literature there is no consensus about the most optimal im injection regimen and the necessity of a loading dose (1-6, 8). Since serum MMA usually drop quickly after injections, our injection regimen has been modified to 3 im scheme without a loading dose.

However, it is not clear whether the shorter injection regimen without a loading dose is just as effective as a longer injection regimen with a loading dose. In this study, we wanted to compare a longer im hydroxocobalamin injection regimen with loading dose with a shorter im hydroxocobalamin injection regimen without loading dose with a follow-up of six months. These 2 regimens will be compared with a control group who had no treatment with im hydroxocobalamin injections. We hypothesized that patients receiving im hydroxocobalamin injections will have higher serum vitamin B12 and lower serum MMA concentrations after six months compared to no injections. Secondly, a regimen with 3 im hydroxocobalamin injections might be as effective as a standard regimen with 6 im hydroxocobalamin injections, although it is not known how long the drop in serum MMA remains after both regimens.

Materials and Methods

In this matched retrospective cohort study, an analysis of serum vitamin B12 and serum MMA in bariatric patients was done. All patients underwent a sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB) either as primary or a revisional procedure, from 2009 to 2015 in the obesity center Catharina Hospital. Data of interest were patient characteristics, baseline serum vitamin B12 and serum MMA and follow-up serum vitamin B12 and serum MMA after six months.

We included 3 groups with complete data sets and baseline selection was done on serum MMA ≥ 300 nmol/L and initial serum vitamin B12 between 140 and 300 pmol/L. During the selection period, all patients were in the postoperative period. Each included group was matched for age, gender, preoperative and current body mass index (BMI) and surgical procedure. Patients with renal insufficiency and type 2 diabetes mellitus were excluded.

All patients were advised to use a MVS daily. Initially, we recommended patients to use a specialized weight loss surgery (WLS) MVS. However, these supplements are more expensive than regular ('over-the-counter') MVS and some patients cannot afford these supplements.

In case of side effects or intolerability for the supplements, a regular MVS was recommended (1, 7, 8). Table 1 gives an overview of both supplements. In total, 16 patients (25,4%) were using WLS MVS, 43 patients (68,3%) were using regular MVS and 4 patients (6,3%) did not use any supplements.

Table 1: Dosage of vitamin B12 in WLS MVS and regular MVS

	Dosage tablets per day	Dosage vitamin B12 in µg per tablet	Dosage vitamin B12 as a percentage per tablet
WLS sleeve	1	10	400%
WLS gastric bypass	1	350	14000%
Regular MVS sleeve	1	2.5	100%
Regular MVS gastric bypass	2	2.5	100%

MVS: multivitamin supplement, WLS: weight loss surgery, µg: microgram

In this study, the intervention consists of im hydroxocobalamin injections. Each injection contains 1000 micrograms of hydroxocobalamin. Group A (n = 21) received 6 im injections with a loading dose of 1 injection every two weeks, during the first 8 weeks. Afterwards, one injection after three months. Group B (n = 21) received 3 im injections in the first, second and third month, without loading dose. Group C (n = 21) received no im injections. Group C was included in order to determine whether serum MMA recover spontaneously over time.

MMA measurement in blood sampling

MMA was measured in EDTA plasma using UPLC-MS/MS (Waters Xevo TQS). Methyl (D3)-malonic acid was used as internal standard.

Mass transitions 116.9 → 73 and 119,9 → 76 were used to quantify these compounds, respectively. Ultrafiltration (Amicon Ultra 0.5 mL – 30K, Millipore) was used as sample preparation and reverse phase chromatography (ACQUITY HSS T3, 100 x 2,1 mm, Waters) was used for separation on UPLC. Evaluation of serum MMA by our institutional laboratory: serum MMA < 300 nmol/L is considered normal, serum MMA between 300- 430 nmol/L is considered moderate deficient and serum MMA > 430 nmol/L is considered severe deficient (7).

Statistical Analysis

Data were retrospectively collected, managed, and analyzed. Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were presented as frequency with percentages. One-way ANOVA (with post-hoc Tukey-b test) was used to compare the baseline serum and follow-up of serum vitamin B12 and serum MMA. To analyze the differences in serum vitamin B12 and serum MMA, the delta was calculated (vitamin B12/ MMA follow-up minus vitamin B12/MMA baseline). These data were also analyzed with the one-way ANOVA test. In all tests, values of $p < 0.05$ were considered statistically significant. Statistical Package for Social Sciences (SPSS, Chicago, IL, USA Version 22.0) for Windows was used to prepare the database and for statistical analysis.

Results

The total post-bariatric patient population consisted of 14 males (22.2%) and 49 women (78.8%) with a mean current BMI of 30.6 ± 8.0 kg/m². Table 2 gives an overview of the baseline characteristics. Biochemical outcomes (serum vitamin B12 and serum MMA) were described in Table 3. Baseline and follow-up serum concentrations of group A and B showed significant differences within both groups ($p = 0.05$ for group A and group B). Serum MMA have been normalized below 300 nmol/L after treatment in all patients of group A. In group B, not all patients improved sufficiently and serum MMA of 6 patients (28.6%) were not normalized below 300 nmol/L after treatment. In group C, a significant increase in serum MMA was observed in the follow-up ($p < 0.05$) (Table 3). In group C, 11 patients (52.4%) had a moderate deficiency (serum MMA between 300 and 430 nmol/L) and 5 patients (23.8%) had a severe deficiency (serum MMA > 430 nmol/L) at baseline. In the follow-up, all patients in group C had serum MMA concentrations above 300 nmol/L, of which 12 patients (57.1%) have had a severe deficiency (serum MMA > 430 nmol/L). There was no significant difference in serum vitamin B12 and serum MMA between 3 groups at baseline. In the follow-up results there is a significant difference in serum vitamin B12 of group A compared to group B ($p = 0.02$), group A compared to group C ($p = 0.03$) and group B compared to group C showed no significant difference ($p = 0.64$).

Table 2: Baseline characteristics (n= 63) (mean ± standard deviation)

Different groups:	Group A	Group B	Group C	*P*-value
Age (years)	43.5 ± 8.6	39 ± 11.9	44.7 ± 9.0	*p* = 0.990
Gender (n):				*p* = 0.616
Male	5	3	6	
Female	16	18	15	
Preoperative body mass index (kg/m²)	40.8 ± 6.6	43.8 ± 7.6	43 ± 6.9	*p* = 0.368
Current body mass index (kg/m²)	28.8 ± 6.2	32.7 ± 12.4	30.5 ± 5.5	*p* = 0.347
Procedures (n):				*p* = 0.905
Sleeve gastrectomy	9	10	8	
Gastric bypass	9	8	8	
Revision surgery	3	3	5	
Time postoperative (n):				*p* = 0.951
≤ 1 year	2	3	3	
2 years	6	9	9	
3 years	7	7	5	
4 years	3	1	2	
5 years	2	1	1	
> 5 years	1	0	1	

In the follow-up results there is also a significant decrease in serum MMA of group A compared to group B ($p = 0.02$), group A compared to group C ($p = < 0.001$) and group B compared to group C ($p < 0.01$) (Table 3).

Table 3: Biochemical effects and serum delta values between of all groups

	Group A	Group B	Group C	*P*-value
Baseline:				
Vitamin B12	200.5 ± 36.0	200.0 ± 45.6	226.2 ± 34.6	NS
MMA	504.0 ± 261.3	455.8 ± 168.1	407.1 ± 156.0	NS
Follow-up:				
Vitamin B12	550.3 ± 451.8	332.9 ± 296.5	211.4 ± 37.6	*
MMA	181.1 ± 64.5	281.7 ± 134.7	514.3 ± 235.9	**
Delta vitamin B12	349.8 ± 454.6	132.9 ± 286.3	-14.8 ± 37.1	***
Delta MMA	-323.0 ± 276.4	-174.1 ± 193.0	107.2 ± 150.8	****

NS: not significant, MMA: methylmalonic acid
*Group A compared to group B (p = 0.02), group A compared to group C (p = 0.003), group B compared to group C (p = 0.64)
** Group A compared to group B (p = 0.02), group A compared to group C (p < 0.001), group B compared to group C (p < 0.01)
***Group A significant increase compared to group C (p < 0.01), group A compared to group B showed no significant difference (p = 0.082), group B compared to group C showed no significant difference (p = 0.388)
**** Group A showed a significant decrease compared to group C (p < 0.01), group A compared to group B showed no significant difference (p = 0.082), group B compared to group C showed a significant difference (p < 0.01)

Delta vitamin B12 and delta MMA

Delta vitamin B12 and MMA was determined by the following calculation: follow up minus baseline concentrations. Table 3 shows delta concentrations of serum vitamin B12 and serum MMA. Serum vitamin B12 was rising faster and serum MMA showed a faster decline in group A ($p < 0.01$).

Sub analysis between different surgical procedures

An overview of differences in baseline and follow-up of serum vitamin B12 and serum MMA per surgical procedure are showed in Table 4. In the SG group, a significant difference in follow-up of serum MMA was observed in group A compared to group C ($p = 0.001$). In the RYGB group, a significant difference in follow-up of serum MMA was observed in group B compared to group C ($p = 0.005$) and group A compared to group C ($p < 0.001$). In the revisional surgery group, a significant difference in baseline serum vitamin B12 was observed in group B compared to group C ($p = 0.016$). A significant difference in follow-up serum MMA was observed in group A and B compared to group C ($p < 0.05$).

Table 4: An overview of differences in baseline and follow-up of vitamin B12 and MMA per surgical procedure

		group A	group B	group C	*P*-value
Sleeve gastrectomy (n= 27, 42.9%)	**Baseline B12**	214.4 ± 27.4	198.0 ± 31.6	232.5 ± 37.3	NS
	Baseline MMA	498.2 ± 123.1	463.7 ± 152.7	354.5 ± 54.8	NS
	Follow-up B12	665.6 ± 507.6	357.0 ± 405.9	206.3 ± 38.9	NS
	Follow-up MMA	188.7 ± 61.3	329.3 ± 165.7	496.9 ± 177.6	*
Gastric bypass (n= 25, 39.7%)	**Baseline B12**	191.1 ± 44.6	220.0 ± 57.1	230.0 ± 37.8	NS
	Baseline MMA	546.6 ± 382.9	403.4 ± 80.5	351.6 ± 100.2	NS
	Follow-up B12	528.4 ± 453.6	337.5 ± 184.8	220.0 ± 46.6	NS
	Follow-up MMA	183.2 ± 77.1	238.9 ± 79.6	377.0 ± 75.3	**
Revision surgery (n= 11, 17.5%)	**Baseline B12**	186.7 ± 20.8	153.1 ± 5.8	210.0 ± 24.5	***
	Baseline MMA	393.7 ± 94.3	569.3 ± 352.5	579.8 ± 223.5	NS
	Follow-up B12	270.0 ± 90.0	240.0 ± 45.8	206.0 ± 19.5	NS
	Follow-up MMA	151.7 ± 35.1	237.0 ± 118.5	761.8 ± 313.5	****

MMA: methylmalonic acid, NS: not significant
* Group C compared to group A (p = 0.001), group B compared to group C (p = 0.065), group B compared to group A (p = 0.132)
** Group C compared to group B (p = 0.005), group C compared to group A (p < 0.001), group B compared to group A (p = 0.459)
*** Group C compared to group B (p = 0.016), group C compared to group A (p = 0.468), group B compared to group A (p = 1.00)
**** Group B compared to group A (p = 1.00), group C compared to group A (p = 0.02), group C compared to group B (p = 0.04)

Discussion

This study showed that all patients with a vitamin B12 deficiency recovered well biochemically after 6 im hydroxocobalamin injections (group A). Some patients were still deficient in group B. Serum MMA cannot recover spontaneously over time in group C without im hydroxocobalamin injection regimen.

In revisional surgery procedures, there was a significant difference in serum vitamin B12 and serum MMA at baseline compared to SG and RYGB procedures. This is caused by the slowly depleted body storage of vitamin B12. After revisional surgery, the vitamin B12 storage may already be exhausted, which possibly results in faster shortage after revision surgery. This may explain the differences at baseline levels in patients with revision surgery. Serum MMA may be increased in renal insufficiency, dehydration and bacterial overgrowth. The intestinal flora produces propionic acid, which is a source of MMA. During antibiotic therapy serum MMA may be lower than normal. Patients suffering from these complaints were not included in this study (13). According to current literature, there is no consensus in terms of the optimal regimen of im hydroxocobalamin injections and the necessity of a loading dose. Secondly, there are inconsistencies in current guidelines about the treatment of vitamin B12 deficiencies (8, 15). Different guidelines and conflicting results in other studies give challenges in clinical practice regarding vitamin B12 treatment. Table 5 gives an overview of the recommended vitamin B12 treatment according to several studies. Only a few studies have a loading dose of vitamin B12 injections in their recommendation. However, our study shows that im injection scheme with loading dose gives better results compared to a shorter and monthly regimen without loading dose.

Table 5: Various literature references and their recommended vitamin B12 treatment

References	vitamin B12 treatment
Levinson et al. 2013	im vitamin B12 1000 µg monthly or 3000 µg every six moths
Bordalo et al. 2011	500 mg/day oral or 1000 mg im per month or 3000 mg im every six months
Clements et al. 2006	1000 µg im every 3 months or intranasal 1000 µg every week
Heder et al. 2010	Treatment first phase: 350 µg /day oral crystalline B12 Treatment second phase: im 1000-2000 µg /2-3 months
Bozkurt et al. 2014	350-600 µg oral vitamin B12 per day is effective in correcting deficiency in 81 to 95% of the patients and im monthly are another option in patient who have trouble adhering to daily oral supplement
Stacy et al. 2010	Neurologic symptoms: im 1000 µg /day for 5 days, followed by 1000 µg per month. In patients who have had gastric bypass surgery: 1000 µg im every 3 months
Aills et al. 2008	Mild malabsorption: oral vitamin cyanocobalamin 500-1000 µg or im 1000 µg daily or every other day for 1 week, then weekly for 4-8 week, and then monthly for life Severe malabsorption: im 1000 µg daily or every other day for 1 week, then weekly for 4-8 week, and then monthly for life

µg: microgram, im: intramuscular

Some limitations need to be addressed. First, it is a small-size retrospective cohort study. Second, bariatric patients use different types of MVS, which may have influence on serum vitamin B12 and serum MMA in general. Whether patients are compliant in taking their MVS is not objectively testable and therefore these data are subjective and prone to potential bias. The body's storage of vitamin B12 is approximately 2000 µg in relation to the recommended daily requirement of 2.4 µg / day.

Approximately 1% of supplemented vitamin B12 will be absorbed passively (by diffusion) along the entire length of the (non-bypassed) intestine after bariatric surgery (8). Rhode et al. (11) found that a dosage of 350 - 600 µg /day of oral vitamin B12 prevented vitamin B12 deficiency in 95% of patients and an oral dose of 500 µg /day was sufficient to overcome an existing deficiency as reported by Brolin et al. (12) in a similar study. However, a lot of our patients use regular MVS with a vitamin B12 dosage of 2.5 or 5 µg /day, for SG or RYGB, respectively. Another important point is the absorption of the im hydroxocobalamin injections; about 10% of the injected dosage is retained (10). A difference in follow-up of serum MMA was also observed between patients who used WLS MVS and patients who used regular MVS. However, the groups of different kind of supplements are too small to do statistical sub analysis. Third, clinical aspects (complaints of vitamin B12 deficiency) are not included in this study because it is not clear which serum MMA correlate with complaints. Basically, this study shows only biochemical normalization and the clinical relevance is questionable. Despite these limitations, the results of the study have demonstrated that a shorter im hydroxocobalamin injection regimen without loading dose is probably not sufficient for all patients in order to treat a vitamin B12 deficiency.

Conclusion

In this study, an im hydroxocobalamin injection with 3 injections without a loading dose is probably not sufficient to treat a vitamin B12 deficiency. An im hydroxocobalamin injection regimen with 6 injections including a loading dose recovered all vitamin B12 deficiencies biochemically. Serum MMA cannot recover spontaneously over time without im hydroxocobalamin injection regimen. Compliance of intake of a MVS and kind supplementation should be considered in decision-making to a certain injection regimen. A randomized clinical trial is necessary to investigate different vitamin B12 supplementation regimens to define the most optimal one and to examine potential placebo effects of im hydroxocobalamin injections and cost effectiveness of the different schedules. Complaints should be included as well to study the clinical relevance.

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CHAPTER 5

Improving bariatric patient aftercare outcome by improved detection of a functional vitamin B12 deficiency

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Abstract

Background

A vitamin B12 deficiency is common after bariatric surgery. Serum vitamin B12 is a poor predictor of the functional vitamin B12 status since deficiencies might even occur within the reference limits. Therefore, vitamin B12 deficiencies with serum vitamin B12 between 140 and 200 pmol/L remain undetected. Serum methylmalonic acid (MMA), however, will detect these deficiencies as accumulates due to functional intracellular vitamin B12 deficiencies. Serum MMA is a relative expensive analysis and is therefore not generally available. To lower the costs, we only request serum MMA when serum vitamin B12 are between these levels. As a result, more biochemical deficiencies were found. However, it was not known whether bariatric patients with serum vitamin B12 between 140 and 200 pmol/L would benefit from supplementation.

Method

Bariatric patients with serum vitamin B12 between 140 and 200 pmol/L with (n = 45) and without (n = 45) intramuscular hydroxocobalamin injection treatment was compared for biochemical effects. To examine whether biochemical benefits of the treatment are correlated with clinical improvement, patient records were checked for complaints.

Results

Treated patients showed a significant increase of serum vitamin B12 ($p < 0.001$) and a significant decrease in serum MMA ($p < 0.001$). Biochemical improvement occurs in both patients with and without clinical symptoms. The control group showed a significant increase of serum MMA ($p < 0.001$). Complaints were disappeared after treatment, while no improvement was observed in untreated patients.

Conclusion

This study showed that all bariatric patients with serum vitamin B12 between 140 and 200 pmol/L benefit clinical and biochemical from intramuscular hydroxocobalamin injections, regardless serum MMA.

Introduction

A vitamin B12 deficiency is common after bariatric surgery (1, 2). A vitamin B12 deficiency can cause various hematologic, gastro-intestinal and neurological disorders. Those occurring in the nervous system appear to be non-specific but left untreated cause permanent damage (3-5). In order to detect these deficiencies as soon as possible, patients are screened for serum vitamin B12 prior and after surgery. For prevention, all patients are started to use an oral multivitamin supplement (MVS) daily from 2 weeks postoperative. However, clinical symptoms of a vitamin B12 deficiency are common despite standard supplementation. Serum vitamin B12 is a poor predictor for functional deficiencies, since deficiencies might be present with serum vitamin B12 above the lower reference limit (LRL, 140 pmol/L) and deficiencies might be absent with serum vitamin B12 below this LRL. Therefore, deficiencies remain undetected when serum concentrations are between 140 and 200 pmol/L (6-8). We use the additional analysis of serum methylmalonic acid (MMA) who quantifies functional shortages (intracellular) since June 2013. Serum MMA is more sensitive and reasonably specific for diagnosis (4-6, 7, 9-14). However, this measurement is not yet used widely, as more complex (expensive) instruments and highly qualified staff is required for this measurement. In order to minimize additional costs, the following approach may be used:

- Only measure serum MMA in patients with serum vitamin B12 in the grey area within the reference values 140-200 pmol/L.
- Start treatment with vitamin B12 in patients with serum vitamin B12 below 200 pmol/L instead of measurement MMA.

In our obesity center all patients with serum vitamin B12 concentrations below 140 pmol/L are always additionally supplemented. Conversely, (very) high serum vitamin B12 do not need to be additionally supplemented (internal research). Since 50% of the patients is in one of these categories, additional serum MMA testing has no benefit for these patients. The first approach, therefore, roughly halved the number of requested serum MMA's. In this study, we want to demonstrate whether vitamin B12 treatment in patients with serum concentration between 140 and 200 pmol/L results in clinical improvement.

Materials and methods

A retrospective analysis of serum vitamin B12 and serum MMA in bariatric patients was done. The Institutional Review Board of the Catharina Hospital Eindhoven approved this study and the study was performed according to de Declaration of Helsinki. All patients underwent a sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB), either as a primary or a revisional procedure, from 2009 to 2014 in the obesity center Catharina Hospital.

Included data were patient characteristics, baseline serum vitamin B12 and serum MMA, complaints such as experienced by patients, check for taking a MVS and an additional check of serum vitamin B12 and serum MMA within twelve months.
The first 45 patients with complete data sets and serum vitamin B12 between 140 and 200 pmol/L received intramuscular (im) hydroxocobalamin injections, regardless of serum MMA. Each injection consists of 1000 mcg hydroxocobalamin (1 injection every 2 weeks for 8 weeks, afterwards 1 injection after three months). In this intervention group we mainly examined serum MMA: the difference between serum MMA before and after treatment. To examine whether biochemical benefits of the treatment are correlated with clinical improvement, patient records were checked for complaints. A vitamin B12 deficiency can cause many mainly subjective symptoms. In our study population we have checked at fatigue in extreme or milder form, tingling fingers and reduced attention span, because we encounter these complaints in daily practice. In order to determine whether serum MMA recover spontaneously over time, we have included a control group of 45 patients with serum vitamin B12 between 140 and 200 pmol/L and comparable in body mass index and distribution of operations. Patients from the control group were selected arbitrarily from the database between June 2013 and August 2013. In this period, we did not yet start vitamin B12 treatment based on serum MMA. This control group did not receive im hydroxocobalamin injections and we mainly examined the difference between serum MMA at baseline and follow-up. Serum MMA < 300 nmol/L is considered normal, serum MMA between 300-430 nmol/L is considered moderate deficient and serum MMA > 430 nmol/L is considered severe deficient in our hospital laboratory (based on internal report of large hospital wide analysis).
All patients are advised to use MVS daily. There is no consensus about the right use of MVS in all guidelines (7, 15). Initially, we recommend patients to use a high-dose weight loss surgery (WLS) MVS. However, these WLS supplements are more expensive than regular ('over-the-counter') MVS and many patients cannot pay these supplements. Also, some patients cannot tolerate these WLS supplements. In this case we recommend a regular MVS (7, 16). The vitamin B12 dosage of these supplements are shown in Table 1. Twenty patients (22.2%) were using WLS MVS, 64 patients (71.1%) were using regular MVS and 6 patients (6.7%) did not use any MVS.

MMA measurement in blood sampling

Methylmalonic acid was measured in EDTA plasma using UPLC-MS/MS (Waters Xevo TQS). Methyl (D3)-malonic acid was used as internal standard. Mass transitions 116.9 - 73 and 119,9- 76 were used to quantify these compounds, respectively.
Ultrafiltration (Amicon Ultra 0.5 mL – 30K, Millipore) was used as sample preparation and reverse phase chromatography (ACQUITY HSS T3, 100 x 2,1 mm, Waters) was used for separation on UPLC.

Table 1: Dosage of vitamin B12 in both supplements

	Dosage tablets per day	Dosage vitamin B12 in μg per tablet	Dosage vitamin B12 (% RDI) per tablet
WLS MVS sleeve	1	10	400%
WLS MVS gastric bypass	1	350	14000%
Regular MVS sleeve	1	2.5	100%
Regular MVS gastric bypass	2	2.5	100%

WLS: weight loss surgery, mg: milligram, MVS: multivitamin supplement, RDI: recommended daily intake, μg: microgram

Statistical analysis

Data were retrospectively collected, managed, and analyzed using SPSS version 22, for Windows (SPSS Inc., IBM Corporation, Armonk, NY, USA). Quantitative data are denoted as mean ± standard deviation. The Chi-square test was used to compare gender, procedures and first MMA measurement between both groups. The Independent t-test and Mann-Whitney U test were used to determine any significance of the observed differences among subgroups. The paired sample t-test was used to determine any significance of the observed differences between baseline and follow-up results in both groups. Statistical significance was identified when the p value was ≤ 0.05.

Results

The patient population consist of 11 men (12.2%) and 79 women (87.8%) with a mean body mass index of 30.2 kg/m². Other baseline characteristics are displayed in Table 2. Twenty-nine patients (64.5%) in the intervention group had a proven functional vitamin B12 deficiency (based on serum MMA >300 nmol/L) at baseline. Treated patients showed a significant increase of serum vitamin B12 from 176.4 ± 27.5 pmol/L to 1067.5 ± 435.1 pmol/L ($p < 0.001$). Serum MMA showed a significant decrease from 413.4 ± 259.4 nmol/L to 129.4 ± 40.1 nmol/L ($p < 0.001$). No functional deficiency was seen after treatment, because all treated patients have serum MMA concentrations below 300 nmol/L. This biochemical improvement occurs in both patients with clinical symptoms and patients without clinical symptoms (Table 3).

Six patients (13%) in the control group had a proven functional vitamin B12 deficiency at baseline (based on MMA > 300 nmol/L). This percentage has risen to 24 patients (53%) in the follow-up. Serum vitamin B12 has remained virtually stable from 176.7 ± 18.0 pmol/L to 178.4 ± 29.5 pmol/L ($p = 0.681$). On the contrary, a significant increase was found between first serum MMA measurement and the follow-up from 178.4 ± 29.5 nmol/L to 322.7 ± 135.9 nmol/L ($p < 0.001$).

Table 2: Baseline characteristics (n = 90) (mean ± SD)

	Intervention group (n = 45)	Control group (n = 45)	*P*-value
Male : female	5 : 40	6 : 39	$p = 1.000$
Age (years)	40.3 ± 9.4	41.6 ± 9.3	$p = 0.568$
Body mass index (kg/ m²)	30.2 ± 5.6	30.2 ± 6.1	$p = 0.611$
Median BMI (kg/ m²)	29.5	27.8	
Procedures (n):			$p = 0.183$
Sleeve gastrectomy	15	24	
Gastric bypass	25	17	
Mini gastric bypass	1	0	
Revision surgery (n):			
AGB to SG	1	1	
AGB to RYGB	2	1	
SG to RYGB	1	2	
Time postoperative (n):			$p = 0.058$
Median time postoperative	0.5	0.5	
0.5 year	28	36	
1- 1.5 years	12	7	
2.5 years	1	2	
3 years	2	0	
4 years	2	0	
First MMA measurement (n):			***p = < 0.001***
MMA < 300 nmol/L	16	39	
MMA 300-430 nmol/L	13	6	
MMA > 430 nmol/L	16	0	

AGB: adjustable gastric band, MMA: methyl malonic acid, SD: standard deviation, SG: sleeve gastrectomy, RYGB: roux-en-Y gastric bypass

Table 3: Biochemical and clinical effects of the intervention group (%)

Biochemical effect	Before im injections	After im injections	*P*-value
Total:			
MMA < 300	35.5%	100%	***p < 0.05***
MMA 300-430	29.0 %	0%	***p < 0.05***
MMA > 430	35.5%	0%	***p < 0.05***
No complaints:			
MMA < 300	22.2%	71.1%	***p < 0.05***
MMA 300-430	24.5%	0%	***p < 0.05***
MMA > 430	24.4%	0%	***p < 0.05***
Complaints:			
MMA < 300	13.3%	28.9%	***p < 0.05***
MMA 300-430	4.5%	0%	***p = 0.22***
MMA > 430	11.1%	0%	
Clinical effect (total patients with complaints)	28.9%	0%	***p < 0.05***

MMA: methylmalonic acid (nmol/L), im: intramuscular

Sub analysis between SG and RYGB

In the follow-up a significant difference in serum vitamin B12 was observed in the intervention group: 1228.7 ± 421.1 pmol/L versus 937.4 ± 427.7 pmol/L, for SG and RYGB respectively (p = 0.034). A significant difference in serum MMA was observed as well in the intervention group: 116.8 ± 37.5 nmol/L versus 141.2 ± 41.9 nmol/L, for SG and RYGB respectively (p = 0.046). The control group did not show a significant difference between SG and RYGB in the follow-up (p = 0.415 and p = 0.989, for vitamin B12 and MMA respectively).

Complaints

Thirteen patients (28.9%) in the intervention group had complaints at baseline (tingling fingers and tired in extreme and milder form). In all patients, complaints were disappeared after treatment (Table 3). Eight patients (18%) in the control group had complaints at baseline (tired in extreme or milder form and reduced attention span). Follow-up results of vitamin B12 related symptoms were unchanged.

Discussion

The control group showed no significant difference in serum vitamin B12 between baseline and follow-up, while serum MMA showed a significant increase. In addition, a severe vitamin B12 deficiency based on serum MMA (> 430 nmol/L) was observed in 35.5% of the patients in the intervention group at baseline (Table 2), which confirmed that serum vitamin B12 itself is a poor predictor of a functional vitamin B12 status. This confirms the necessity for the measurement of additional parameters. Vitamin B12 assays that are currently used to diagnose clinical vitamin B12 deficiency have a failure rate of 22 to 35% and clinicians may not recognize the deficiency (9, 10). This failure rate may be due to the fact that 80% of the serum vitamin B12 is bound to the transport protein haptocorrin (17-19). This percentage is biologically unavailable and cannot be absorbed by the cells, which means that serum vitamin B12 concentrations poorly correlate with the bioavailable intracellular vitamin B12 content. Holotranscobalamin, a blood serum transport protein, binds the remaining 20% of the vitamin B12. Only holotranscobalamin can bind a specific receptor on the cell and ensure the supply of vitamin B12 (3, 4, 20-22). Moreover, serum MMA may be also increased in renal insufficiency, dehydration and bacterial overgrowth. The intestinal flora produces propionic acid; which is a source of MMA. During antibiotic therapy serum MMA may be lower than normal (23-25). Patients suffering from these complaints were not included in this study.

This study had certain limitations. First, a significant difference in serum MMA was observed in both groups at baseline. However, we only included a control group in order to determine whether serum MMA recovers spontaneously over time. Second, there is a big difference in procedures between both groups. Therefore, a sub analysis was performed. The sub analysis has shown higher serum vitamin B12 and lower serum MMA after treatment in SG procedures, in comparison with RYGB procedures. This is caused by surgical techniques who affect the absorption of vitamin B12. Sleeve patients have reduced production of stomach acid and reduced availability of intrinsic factor (IF). In gastric bypass patients a vitamin B12 deficiency due to loss of IF and acid secretion in the stomach is expected. The remnant stomach and duodenum are eliminated from the digestion process as well (1, 2, 11, 27). A vitamin B12 deficiency can also develop years after the surgery when the liver stocks are slowly depleted (10, 28). In patients with revision surgery the vitamin B12 storage may already be exhausted which possibly results in faster shortage after revision surgery. This group was not included in the sub analysis, because this group was too small. However, all patients normalize biochemically (serum MMA <300 nmol/L) and complaints were disappeared after treatment, irrespective of the different surgical techniques. Third, bariatric patients use different types of MVS what may have little influence on serum vitamin B12 or serum MMA generally. However, these data were subjectively and it is unclear if patients take their supplements daily. Fourth, no questionnaires were used to detect complaints in this retrospective study. Data of complaints were not collected consistently. However, normalization of serum MMA irrespective of the presence of clinical symptoms, suggests that clinical symptoms are no good read-out to assess vitamin B12 treatment makes sense. This suggests that objectify the vitamin B12 status with laboratory diagnostics periodically makes always sense despite a good history of complaints. Despite these limitations, the results of the study have demonstrated that determination of vitamin B12 is not sufficient and complaints are resolved in all treated patients.

Conclusion

This study shows that all vitamin B12 deficient patients benefit from treatment with im hydroxocobalamin injections. However, also positive results were found for patients without a functional vitamin B12 deficiency (serum MMA < 300 nmol/L), suggesting that supplementation itself, regardless the actual vitamin B12 status improves clinical symptoms. Furthermore, if serum MMA is included in the diagnostics, we find more functional vitamin B12 deficiencies. We can treat vitamin B12 deficiencies earlier and possibly prevent complaints. A diagnostic algorithm with serum vitamin B12 plus serum MMA might help to identify patients who benefit most, at reasonable low costs. Furthermore, this study suggests that increasing the cut-off level of serum vitamin B12 for im treatment to 200 pmol/L might be an alternative way to reduce deficiencies and costs. A double-blind intervention study is required to examine potential placebo effects of im hydroxocobalamin injections and cost effectiveness of measuring serum MMA versus treatment with im treatment.

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CHAPTER 6

Assessment of physical fitness after bariatric surgery and its association with protein intake and type of cholecalciferol supplementation

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Abstract

Background

Several studies showed that there is a relationship between vitamin and mineral status and muscle strength. In particular this is the case for handgrip strength (HS) and vitamin D deficiencies. After bariatric surgery, there is a risk on the development of vitamin deficiencies and decrease in muscle strength. The aim of this study is to assess the effect of low serum 25-hydroxyvitamin D concentrations, 2 different cholecalciferol supplementation regimens and protein intake on physical fitness.

Methods

For this retrospective study, 100 patients who have had bariatric surgery were included. Group A (n = 50) used 800 IU oral cholecalciferol per day. Group B (n = 50) used 800 IU oral cholecalciferol daily and 50,000 IU cholecalciferol once per month. Both groups were matched on common variables. To measure physical fitness, we used the HS manometer of Jamar and the shuttle walk run test (SWRT) to assess physical capacity. The protein intake was calculated with a 24-hour food intake registration by the clinical dietician.

Results

No significant differences in HS and SWRT outcomes were found between patients with serum 25-hydroxyvitamin D < 75 nmol/L or > 75 nmol/L. The postoperative HS was significantly influenced by protein intake ($p = 0.017$), but no significant influence was observed in the SWRT outcomes ($p = 0.447$).

Conclusion

We have found that serum 25-hydroxyvitamin D and different cholecalciferol supplementation regimens did not have a significant effect on HS and SWRT after bariatric surgery. It seems that protein intake plays a more important role in maintaining adequate muscle strength.

Introduction

Obesity and associated comorbidities are growing worldwide to epidemic proportions and bariatric surgery is the only established treatment that provides long-lasting weight reduction and a significant decrease in mortality and morbidity (1). Some of the available literature suggests that bariatric surgery may also induce bone loss, despite adequate supplementation of vitamins and minerals. Some of the 'post-bariatric' patients may develop osteopenia, osteomalacia and osteoporosis (2). In states of malnutrition, impaired muscle strength can also occur. Because of a low nutritional intake (especially proteins) after bariatric surgery, this may lead to a compensatory loss of (muscle) protein that is preferably lost from muscle mass, the body's largest protein reserve (3). Consequently, a reduction in muscle strength is associated with loss of physical capacity and function and also has a negative impact of recovery, especially after surgery. This explains the predictive aspects of muscle function tests, in particular the association between low muscle strength and the occurrence of complications (4). Promoting physical capacity and fitness is essential in the current obesity treatment, but also before and after bariatric surgery. The goal of preoperative and postoperative physical therapy is to avoid distinctive muscle atrophy, which is an essential part of the postoperative care (3). Also, as pointed out by the study of Gumieiro et al., lower handgrip strength (HS) is associated with a vitamin D deficiency (5). In our obesity center, shuttle walks run test (SWRT) and HS measurement is included in the perioperative care of bariatric surgical patients.

Vitamin D is pivotal for a good musculoskeletal and bone health (6). Vitamin D deficiencies are often asymptomatic. In case of muscle weakness there is often a vitamin D deficiency and vica versa (6). There is emerging consensus that serum 25-hydroxyvitamin D from ≥ 75 - 80 nmol/L are optimal for both bone health and skeletal benefits (7). However, there are no procedure specific guidelines on how to achieve this target in patients following bariatric surgery. Maniscalo et al. assessed the magnitude of difference in walking capacity and perceived symptoms in obese subjects after bariatric surgery (8). An improvement of distance walked in 6 minutes was observed 1 year after surgery. However, the effect of serum 25-hydroxyvitamin D and protein intake on these results has not been included.

Our standard postoperative supplementation regimen consists of 800 IU oral cholecalciferol and 1000 mg calcium carbonate daily. Additional supplementation with cholecalciferol 50,000 IU once per month was deployed since January 2016, because vitamin D deficiencies exist frequently with the standard supplementation regimen. However, it is unclear whether this change in cholecalciferol dosage affected the outcomes of physical fitness of bariatric patients. The aim of this study is to assess the effect of two different cholecalciferol supplementation regimens and protein intake on physical fitness, measured using the HS and the SWRT. We hypothesized:

- Low serum 25-hydroxyvitamin D concentrations affect muscle strength and physical fitness and will result in a lower HS and decreased SWRT distance.
- A high dose of cholecalciferol monthly in addition to a standard daily dose gives better results regarding HS and SWRT distance.
- Higher protein intake improves the results regarding HS and SWRT distance.

Materials and Methods

For this retrospective study we used a cohort of 100 patients who have had bariatric surgery in the period of November 2015 until January 2016. All patients underwent a sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB) procedure, in our obesity center. Patients with kidney disease or gastro-intestinal disorders were excluded from this study.
Group A (n = 50) used oral cholecalciferol supplementation with 800 IU per day. Group B (n = 50) used oral cholecalciferol supplementation with 800 IU daily and 50,000 IU cholecalciferol once per month. Both groups were matched for age, gender, preoperative body mass index (BMI), current BMI and surgical procedure. This study was approved by the Institutional Review Board of the Catharina Hospital Eindhoven (research registry database number 4944) and adheres the principles laid down in declaration of Helsinki in 1964.

Biochemical measurement and correction of vitamin D deficiency preoperatively

Serum 25-hydroxyvitamin D concentrations were measured three months preoperatively and six months postoperatively. In addition, as a part of our treatment protocol, serum calcium and PTH were measured as well. A vitamin D deficiency was defined as a serum 25-hydroxyvitamin D < 75 nmol/L. Reference values of serum calcium were between 2.10 and 2.55 mmol/l and for serum PTH between 1.6 and 6.9 pmol/L. Preoperative serum 25-hydroxyvitamin D below 75 nmol/L were treated with cholecalciferol 50,000 IU per week for 6 weeks and afterwards once per month up to the bariatric procedure.

Handgrip Strength (HS)

The maximum grip strength of the hand is a good indication of the muscle function (1, 4). The muscle strength was evaluated by measuring the HS with the JAMAR hydraulic hand dynamometer (Lafayette Instruments, USA). Patients were asked to sit on a comfortable chair with form armrests on which. The elbow of the patient was flexed at 90º and they were asked to squeeze the force meter with their preferred hand for approximately two seconds. Two measurements per patient were done. After each measurement the pointer of the meter was turned to zero and the best value was record. The HS was measured preoperatively, three months and six months postoperatively. Table 1 gives an overview of HS meter references in kilogram-force (kgf) (9).

Table 1: Handgrip strength meter references in kilogram-force

Age	Female	Male
15	28	42
20	29	43
25	30	44
30 - 45	30	45
50	29	45
55	28	44
60	27	43
65	25	41

Shuttle Walk Run Test (SWRT)

The SWRT is a reliable and valid test by repeatedly measuring the submaximal exercise functional capacity (10, 11). Patient runs up and down between 2 lines in a range of 10 meters. The walking pace is indicated by a beep of a sound system. The patient leaves the first line as soon as the signal sound. Patient walks to the second line where the patient should have arrived at the following sound. Per minute, the walking speed is increased by shortening the time between beeps. The test ends when the patient is too late two times in a row, or the rate cannot be maintaining anymore. Outcome measurements are shown in metabolic equivalent of time (MET). MET's have been determined for a wide variety of activities and are specific to that particular physical activity (12). Each MET stage has been related to a particular level, speed in kilometers per hour and a distance in meters (Table 2).

The SWRT was done preoperatively, three months and six months postoperatively. For our bariatric patients, the SWRT conform the Bradley protocol was used (12).

Table 2: Metabolic Equivalents of Time references of a modified shuttle walk test (12)

MET score	Level	Speed in km/hour	Distance (meter)
2,5	Level 3	3.0	80-120
3.0	Level 4	3.6	130-180
3.5	Level 5	4.2	190-250
4.0	Level 6	4.8	260-330
5.0	Level 7	5.4	340-420
5.5	Level 8	6.0	430-520
6.0	Level 9	6.6	530-630
6.5	Level 10	7.2	640-750
7.0	Level 11	7.8	760-880
8.0	Level 12	8.4	890-1020
9.0	Level 13	9.0	1030-1170

Protein intake

Recommended protein intake was calculated conform the AACE/ASMBS guidelines to 1.0 gram per kilogram ideal body weight (body mass index of 22.5 kg/m²) to a minimum of 60 gram per day (13). A 24-hour food intake registration was done by a clinical dietician three and six months postoperatively.

Statistical analysis

Data were retrospectively collected, managed, and analyzed using SPSS version 20, for Windows (SPSS Inc., IBM Corporation, Armonk, NY, USA). Quantitative data are denoted as mean ± standard deviation. Categorical variables were presented as frequency with percentages and the chi-square was used to compare these data. Data distribution was determined by assessing the skewness and kurtosis. Depending on the data distribution, either parametric tests (independent t-test, or student's t-test) or non-parametric tests (Mann Whitney-U) were used to analyze the results. To assess the effect of protein intake on postoperative outcomes of the SWRT and HS a multivariate analysis was used. P-values ≤ 0.05 were considered statistically significant.

Results

Table 3 shows the baseline characteristics of both patient groups.

Table 3: Baseline characteristics (n=100) (mean ± SD)

	Group A	Group B	*P*-value
Age (years)	43.8 ± 11.6	47.5 ± 9.7	$p = 0.075$
Gender (n) **Male: female**	9: 41	10: 40	$p = 0.799$
Preoperative body mass index (kg/m²)	42.6 ± 5.7	42.5 ± 5.2	$p = 0.911$
Current body mass index (kg/m²)	31.8 ± 4.6	31.7 ± 4.6	$p = 0.879$
Procedures (n)			$p = 0.359$
SG	28	29	
RYGB	18	20	
Revision surgery	4	1	

SG: Sleeve gastrectomy, RYGB: Roux-en-Y Gastric Bypass, SD: standard deviation

In group A, a significance difference was observed in serum calcium preoperative (2.37 ± 0.08 mmol/L) and six months postoperative (2.39 ± 0.08 mmol/L) ($p = 0.058$). In group B, no significant difference was observed in serum calcium preoperative (2.38 ± 0.11 mmol/L) and six months postoperative (2.38 ± 0.09 mmol/L) ($p = 0.930$). Mean serum PTH in group A were 7.5 ± 3.1 pmol/L preoperative and 6.5 ± 2.9 pmol/L six months postoperative ($p = 0.032$). Mean serum PTH in group B were 6.8 ± 2.7 pmol/L preoperative and 5.2 ± 1.6 pmol/L six months postoperative ($p < 0.001$). In group B there was much more pronounced decrease in serum PTH after six months (probably due to higher doses of cholecalciferol supplementation). Serum 25-hydroxyvitamin D increased from 37.8 ± 20.6 nmol/L to 66.7 ± 18.5 nmol/L and from 47.0 ± 21 to 94.2 ± 25.7, for group A and B respectively ($p = 0.001$ for both groups). Of all patients, 59 completed the HS preoperatively, 93 completed it three months postoperatively, and 99 patients completed the test six months postoperatively. Fifty-eight patients completed the SWRT preoperatively and 84 patients at six months postoperatively.

Handgrip strength

HS outcome measurements of group A and B pre- and postoperatively are shown in Table 4. No significant differences were found between group A and B postoperatively ($p = 0.439$). No significant differences in HS outcomes were found between patients with serum 25-hydroxyvitamin D < 75 nmol/L or > 75 nmol/L (Table 5).

Table 4: Comparing HS and SWRT outcomes of group A and B preoperatively

HS	Preoperatively	3 months postop	6 months postop	*P*-value
HS group A	33.7 ± 12.2	32.2 ± 9.3	32.2 ± 8.0	*
HS Group B	36.3 ± 9.8	34.1 ± 10.9	33.8 ± 10.2	**
SWRT group A	5.2 ± 1.1	6.1 ± 1.5	6.7 ± 1.5	***
SWRT group B	5.2 ± 1.1	6.0 ± 1.6	6.7 ± 1.5	****

HS: handgrip strength, SWRT: shuttle walk run test, SD: standard deviation
*: preoperative HS compared to HS 3 months postoperative (p = 0.301), preoperative HS compared to 6 months postoperative (p = 0.052), HS 3 months postoperative compared to HS 6 months postoperative (p = 0.078)
** : preoperative HS compared to HS 3 months postoperative (p = 0.040), preoperative HS compared to 6 months postoperative (p = 0.058), HS 3 months postoperative compared to HS 6 months postoperative (p = 0.018)
***: preoperative SWRT compared to SWRT 3 months postoperative (p = 0.06), preoperative SWRT compared to 6 months postoperative (p = 0.07), SWRT 3 months postoperative compared to SWRT 6 months postoperative (p < 0.001)
****: preoperative SWRT compared to SWRT 3 months postoperative (p < 0.001), preoperative SWRT compared to 6 months postoperative (p < 0.01), SWRT 3 months postoperative compared to SWRT 6 months postoperative (p = 0.005)

Shuttle walk run test

SWRT outcome measurements of group A and B pre- and postoperatively are shown in Table 4. No significant differences were found between group A and B postoperatively ($p = 0.517$). No significant differences in SWRT outcomes were found between patients with serum 25-hydroxyvitamin D < 75 nmol/L or > 75 nmol/L (Table 5).

Protein intake

An adequate protein intake was calculated in 34 patients (68%) of group A and 41 patients (82%) of group B. The remaining 16 patients (32%) in group A and 9 patients (18%) in group B had a protein intake below 60 grams per day.

Using a multivariate analysis, the postoperative HS was significantly influenced by protein intake (p = 0.017). The influence of protein intake on postoperative SWRT outcomes was not significant (p = 0.447).

Table 5: Differences in HS and SWRT outcomes (mean ± SD)

HS	Vitamin D < 75 nmol/L	Vitamin D > 75 nmol/L	*P*-value
Preoperatively			
Group A	34.2 ± 12.7	29.5 ± 6.4	p = 0.842
Group B	36.4 ± 10.4	35.2 ± 4.4	p = 0.874
6 months postoperatively			
Group A	32.4 ± 9.0	31.8 ± 5.3	p = 0.799
Group B	37.3 ± 7.6	32.8 ± 10.7	p = 0.110
SWRT	**Vit D < 75 nmol/L**	**Vit D > 75 nmol/L**	***P*-value**
Preoperatively			
Group A	5.1 ± 1.4	5.0 ± 0.0	p = 0.842
Group B	5.2 ± 1.3	5.8 ± 1.5	p = 0.474
6 months postoperatively			
Group A	6.9 ± 1.6	6.2 ± 1.1	p = 0.096
Group B	6.6 ± 1.3	6.4 ± 1.6	p = 0.923

HS: handgrip strength, SWRT: shuttle walk run test, SD: standard deviation

Discussion

This study aimed to assess the effects of two different cholecalciferol supplementation regimens of physical fitness measured with the HS and the SWRT. Outcomes of HS and SWRT were not significantly influenced by serum 25-hydroxyvitamin D and it seems that protein intake plays a more important role in maintaining adequate muscle strength. An inadequate protein intake was significantly associated with outcomes of the HS, but not with the SWRT. This suggests that the protein intake is obviously very important in terms of muscle strength but might be less important in terms of physical capacity. The results of our study contradict the study by Gumiero et al. who described a lower HS in patients with a vitamin D deficiency and the study by Cangussu et al. who reported muscle loss in vitamin D deficient patients (5, 6). This indicated the important role of vitamin D in bone and musculoskeletal health. However, in our study no significant differences were found between patients with serum 25-hydroxyvitamin D < 75 nmol/L and serum 25-hydroxyvitamin D > 75 nmol/L. On a histological level, myopathic changes were observed in muscle biopsy specimens of morbidly obese patients after two weeks of starvation (4).

Also, several reports on fat-free mass loss (FFML) in bariatric surgery showed that there is muscle loss after surgery (4, 14). These findings were substantiated by a review of Chaston et al. indicating that bariatric surgery results in greater FFML than very low-calorie diets (14). The amount of %FFML is different among several bariatric surgical procedures. The greatest %FFML was found in Biliopancreatic Diversion and RYGB procedures compared to adjustable Gastric Band in the same review (14). Unfortunately, no data was presented about the SG.
The aforementioned findings might be an explanation for the significant decrease in HS in the postoperative period. The findings were corroborated by a recent study by Pouwels et al. that showed a significant decrease of respiratory muscle strength after bariatric surgery (15). However, it is difficult to assess one factor that is responsible for these changes. The metabolic changes after bariatric surgery are mainly multifactorial. This was also shown in a study by Berggren et al. indicating that obese patients have an impaired beta- oxidation of lipids, that significantly improved by exercise training (16). The study of Stegen et al. showed that a three times per week endurance and resistance exercise program could prevent this decrease and even induce an increase in muscle strength in the first four months postoperatively, but the influence of protein intake was not included (3). The study of Davies et al. describes that protein loss in gastric restrictive procedures is considerably lower than in malabsorptive procedures (17). However, protein malnutrition and a decrease in fatty: lean mass ratio of 4:1 in certain restrictive procedures has also been reported in this study. The incidence of protein malnutrition in all purely restrictive procedures is between 0- 2% and in all malabsorptive procedures between 13.4- 18% (17).

Clinical implications of handgrip strength

Since muscle function reacts earlier to nutritional deprivation as well as restoration than muscle mass, it is obviously very tempting to employ HS as target for detecting and monitoring changes in nutritional status (4). HS is a simple, noninvasive marker of the muscle strength of the upper extremities, which is well suitable for clinical practice. This parameter is easy to measure, resulting in only minimal costs. Moreover, an increasing number of studies have shown the predictive value of HS with regard to mortality and morbidity in a variety of clinical conditions (1). Improvement in muscle function is usually accompanied by improved functional status. Norman et al. showed an improvement in HS in the intervention group of malnourished patients with benign gastro-intestinal disease (1). This intervention group have had oral nutritional supplements for three months and results were significantly correlated to physical function (1). Beattie et al. examined oral nutritional supplements for 10 weeks in malnourished surgical patients (18). Postoperative HS reduction in intervention patients was less marked, with significantly improved values at ten weeks when compared with controls (18). Ha et al. showed a significantly higher increase of HS in malnourished stroke patients with nutritional support for three months (19). Paton et al. reported significant increase in fat free mass and HS in malnourished tuberculosis patients after six weeks intervention with sip feeds (20). All these results confirmed the necessity for a good nutritional status and adequate protein intake. In comparison to the other studies, the study of Otto et al. showed no significant changes in HS during the first four months after bariatric surgery (1). Nevertheless, the preoperative HS showed a strong positive correlation with the postoperative body composition, but the protein intake was not included (1). Besides that, age and gender are the strongest influencing factors on HS in healthy people (4). However, the influence of gender and age has never been investigated in the bariatric target group. In our study, the study population is too small to perform an adequate sub analysis.

Clinical implications of the Shuttle Walk Run Test

The outcomes of SWRT in both groups were significantly increased after three and six months. No significant differences between both groups were found which suggests that different cholecalciferol supplementation regimen seem to have a little impact on these outcomes. Multiple studies have shown that the SWRT is a reliable indicator for the assessment of cardiopulmonary fitness (17-20). The study of Goncalves et al. showed that female gender, older age and lower heart rate before the test are the determinants of not reaching maximal effort (22). In the current literature the SWRT and other measurement properties are widely used to determine the exercise capacity in a variety of diseases, however, there is no consensus which one is the (possible) gold standard (10-12). In current bariatric practice exercise capacity is measured by either objective measurement such as exercise bouts (23) and also by questionnaires (24). In future research we need to assess possible differences in properties to measure exercise capacity and it correlates with clinically relevant outcome measurements (e.g., vitamin status and protein intake).

Limitations

Despite the promising findings in this study, we also need to discuss limitations. First, this was purely a retrospective study, which can give bias despite adequate matching of both groups. Second, to really study the effects on muscle strength we also need to take into account other vitamins and minerals that play a pivotal role in musculoskeletal health. Third, the effects on clinical outcomes need to be studied in a larger and better designed randomized study including DEXA scans. Due to small numbers in this study, the differences between SG and RYGB were not studied.

Conclusion

We have found that different cholecalciferol supplementation regimens do not have a significant effect on physical fitness measured with the HS and SWRT. Both were not significantly influenced by low or normal serum 25-hydroxyvitamin D. It seems that protein intake plays a more important role in maintaining adequate muscle strength.

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CHAPTER 7

The influence of different cholecalciferol supplementation regimens on 25-hydroxyvitamin D, calcium and parathyroid hormone after bariatric surgery

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Abstract

Background

Vitamin D is an essential vitamin that plays a key role in maintaining physiological calcium balance and is also a pivotal element in the formation of bone structure. A vitamin D deficiency is associated with a wide array of clinical symptoms. Vitamin and mineral deficiencies are quite common prior to and after bariatric surgery, and therefore we have evaluated the biochemical effects of two different cholecalciferol supplementation regimens on serum calcium, 25-hydroxyvitamin D and parathyroid hormone (PTH).

Methods

In this retrospective matched cohort study, two different cholecalciferol supplementation regimens were compared. Group A (n = 50) received 1000 mg calcium carbonate and 800 IU cholecalciferol daily. Group B (n = 50) received 1000 mg calcium carbonate and 800 IU cholecalciferol daily and 50,000 IU cholecalciferol once per month. The primary outcome measurements were the biochemical effects on serum calcium, 25-hydroxyvitamin D and PTH.

Result:

In group A and group B, there were significant increases in serum 25-hydroxyvitamin D, with a higher delta in favor of group B (for all three $p < 0.001$). Significant decreases in both groups were observed in serum PTH ($p < 0.001$). No significant differences were measured in serum calcium in both groups.

Conclusion

Our study suggests that a daily regimen with 1000 mg calcium carbonate and 800 IU cholecalciferol with an additional dose of 50,000 IU cholecalciferol once per month result in less biochemically 25-hydroxyvitamin D deficient patients after bariatric surgery. No effects were observed on the calcium balance. However, larger randomized clinical trials need to be done to assess the effects on clinical outcomes like bone health and fracture risk on long term.

Introduction

In general, vitamin D is part of the complex physiology maintaining calcium balance and bone structure, but also aids in the absorption of calcium from the intestine and reabsorption in the distal renal tubules (in presence of parathyroid hormone (PTH)). Vitamin D deficiencies can increase the risk of osteoporosis and fractures, but also have effects on the immune system and muscle strength (1). A vitamin D deficiency is often accompanied by a reduced dietary calcium intake, but this does not necessarily affect the serum calcium (1, 2). Physiologically, when there is a fluctuation in serum calcium, PTH will also fluctuate. In case of a decreased serum calcium, PTH will increase (1, 2). Clinical symptoms of a hypocalcemia can vary, but symptoms like leg cramping, tetany, and neuromuscular hyper excitability are often reported (2).

Vitamin D deficiencies are common in bariatric surgical practice, and the reported prevalence prior to surgery varies between 54% and 80% (3). In patients with obesity, this is often a combination of several problems: 1) limited sun exposure, 2) decreased bioavailability of vitamin D due to sequestration in the excess fatty tissue, and 3) inadequate dietary intake of vitamins and minerals (3). A secondary hyperparathyroidism can also contribute negatively because it results in increased 25-hydroxyvitamin D hydroxylation, and therefore decreasing vitamin D (2, 3). In addition to hyperparathyroidism, several cases of osteomalacia have been described following bariatric surgery (4, 5). It needs to be taken into account that these are rare phenomena.

Currently, it is advised by several guidelines that serum 25-hydroxyvitamin D ≥ 75- 80 nmol/L are optimal, especially for patients before and after bariatric surgery (6, 7). However, if deficiencies occur, there is no consensus on how we should supplement these patients to achieve normal serum 25-hydroxyvitamin D concentrations. In our bariatric practice, we have used several supplementation regimens. One of them was 1000 mg oral calcium carbonate and 800 IU oral cholecalciferol daily. Unfortunately, too many patients remained deficient after this regimen, and therefore we added additional cholecalciferol 50,000 IU once per month to our supplementation protocol. However, it is unclear whether this switch has the desired effects on serum 25-hydroxyvitamin D, PTH and calcium. We aimed to evaluate the effects of these supplementation regimens on serum 25-hydroxyvitamin D, calcium and PTH. Therefore, we hypothesize that a supplementation regimen of 800 IU oral daily and 50,000 IU monthly leads to higher serum 25-hydroxyvitamin D concentrations and less vitamin D deficiencies.

Materials and Methods

In this retrospective study we included 100 patients who have had bariatric surgery in the period of June 2015 until January 2016.

All patients underwent a sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB) either as primary or a revisional procedure, in the obesity center Catharina Hospital Eindhoven. In case of RYGB, an alimentary limb length of 150 cm and a biliopancreatic limb length of 75 cm were used. Patients with kidney disease or gastro-intestinal disorders were excluded from this study. The included patients from group A (n = 50) were selected on the operation date in June 2015 and these patients received 1000 mg calcium carbonate and 800 IU cholecalciferol daily. The included patients from group B (n = 50) were selected on the operation date in January 2016 and these patients received the previous mentioned supplementation regimen and 50,000 IU cholecalciferol once per month. Both groups were matched for age, gender, preoperative body mass index (BMI), current BMI and surgical procedure.

Biochemical measurements and correction of vitamin D deficiency preoperatively

Baseline blood analysis of all patients were done preoperatively and six months postoperatively. For this study, serum calcium, 25-hydroxyvitamin D and PTH were assessed. A vitamin D deficiency was defined as serum 25-hydroxyvitamin D < 75 nmol/L. Reference values of calcium and PTH were 2.10 - 2.55 mmol/L and 1.6 - 6.9 pmol/L, respectively. Preoperative vitamin D deficiencies in all patients were treated with 50,000 IU cholecalciferol once per week for six weeks and afterwards 50,000 IU cholecalciferol monthly up to the bariatric procedure.

Statistical analysis

Data were collected, managed, and analyzed using SPSS version 22, for Windows (SPSS Inc., IBM Corporation, Armonk, NY, USA). Quantitative data are denoted as mean ± standard deviation (SD). Categorical variables were presented as frequency with percentages. The chi-square test was used to compare categorical variables among groups. Distribution of data was verified using the Shapiro-Wilks test. Depending on distribution, the paired t-test was used for parametric data and the Mann-Whitney U test for non-parametric data. To analyze differences in serum calcium, 25-hydroxyvitamin D, and PTH, the delta was calculated (follow-up minus baseline) and these values were compared between groups using the one-way ANOVA test. A p-value ≤ 0.05 was considered statistically significant.

Results

Table 1 gives an overview of the baseline characteristics of both groups. None of the included patients had symptoms of a hypocalcemia.

Table 1: Baseline characteristics (mean ± SD)

Different groups	Group A (n = 50)	Group B (n = 50)	P-value
Age (years)	43.8 ± 11.6	47.5 ± 9.7	$p = 0.075$
Gender (n) **Male : female**	9 : 41	10 : 40	$p = 0.799$
Preoperative body mass index (kg/m²)	42.6 ± 5.7	42.5 ± 5.2	$p = 0.911$
Current body mass index (kg/m²)	31.8 ± 4.6	31.7 ± 4.6	$p = 0.879$
Procedures (n)			$p = 0.359$
- SG	28	29	
- RYGB	18	20	
- Revision surgery	4	1	

SG: Sleeve gastrectomy, RYGB: Roux-en-Y Gastric Bypass, SD: standard deviation

Serum 25-hydroxyvitamin D, calcium and PTH

Both groups showed an increase in serum 25-hydroxyvitamin D in the follow-up ($p < 0.001$ for group A and B) (Table 2). Of all included patients, 91 patients (91%) have had a vitamin D deficiency (< 75 nmol/L) preoperatively. In group A, 47 patients (94%) have had a vitamin D deficiency at baseline and 35 patients (70%) in the follow-up. In group B, 44 patients (88%) have had a vitamin D deficiency at baseline and 10 patients (20%) in the follow-up. No differences were observed in serum calcium in group A ($p = 0.058$) and group B ($p = 0.930$). Decreases in PTH were seen in the follow-up in group A ($p < 0.032$) and group B ($p < 0.001$) (Table 2).

7

Table 2: Overview of the baseline and postoperative biochemical outcomes (mean ± SD)

	Serum measurement	Preoperative serum outcome	Postoperative serum outcome	P-value
Group A	**25(OH) cholecalciferol**	37.8 ± 20.6	66.7 ± 18.5	***p* < 0.001**
	PTH	7.5 ± 3.1	6.5 ± 2.9	***p* = 0.032**
	Calcium	2.37 ± 0.08	2.39 ± 0.08	$p = 0.058$
Group B	**25(OH) cholecalciferol**	47.0 ± 21.5	94.2 ± 25.7	***p* < 0.001**
	PTH	6.8 ± 2.7	5.2 ± 1.6	***p* < 0.001**
	Calcium	2.38 ± 0.11	2.38 ± 0.09	$p = 0.930$

PTH: Parathyroid Hormone, SD: standard deviation

Delta (Δ) of 25-hydroxyvitamin D, PTH and calcium

A significant difference in delta 25-hydroxyvitamin D was observed between group A (28.9 ± 16.7 nmol/L) and group B (47.2 ± 24.3 nmol/L), in favor of group B ($p < 0.01$). Delta PTH was not significant between both groups (-1.0 ±-0.3 and-1.6 ±-1.1, for group A and B respectively) ($p = 0.336$). No significant difference was observed in delta calcium ($p = 0.185$).

Sub analysis between SG and RYGB

In group A, no preoperative significant differences were found in serum 25-hydroxyvitamin D (p = 0.573), calcium (p = 0.341) and PTH (p = 0.995) between SG and RYGB.
No significant differences were found in serum outcomes between SG and RYGB six months after surgery (p = 0.851, p = 0.080 and p = 0.482, for 25-hydroxyvitamin D, calcium and PTH, respectively). In group B, no preoperative significant differences were found in serum 25-hydroxyvitamin D (p = 0.970), serum calcium (p = 0.796) and serum PTH (p = 0.127) between SG and RYGB. No significant differences were found between SG and RYGB six months after surgery (p = 0.984, p = 0.615 and p = 0.992, for 25-hydroxyvitamin D, calcium and PTH, respectively).

Discussion

A standard supplementation regimen with 1000 mg calcium carbonate, 800 IU cholecalciferol daily and 50,000 IU cholecalciferol monthly leads to less deficiencies and a faster decline of PTH. There is no consensus about the right dose of vitamin D supplementation after bariatric surgery (8, 9). The recommended dosage of elemental calcium ranges from 1200 to 2000 mg daily (2, 10, 11). Supplementation with 400 – 800 IU cholecalciferol might not provide adequate protection for postoperative patients against an increase in PTH and bone resorption (12, 13). In the study of Flores et al., 56% of the bariatric patients had serum 25-hydroxyvitamin D concentrations > 75 nmol/L one year postoperatively by using 2000 IU cholecalciferol daily (14). Goldner et al. describes serum 25-hydroxyvitamin D concentrations > 75 nmol/L in 44% of the patients with 800 IU cholecalciferol daily and in 78% of the patients with 2000 IU cholecalciferol daily (15, 16). In our study, the cholecalciferol supplementation regimen with 800 IU cholecalciferol was simply not enough to biochemically restore serum 25-hydroxyvitamin D in 70% of the patients. However, 20% of the patients were still having a deficiency with 800 IU cholecalciferol daily and 50,000 IU cholecalciferol monthly. This high-dose cholecalciferol regimen gives better results in terms of a more prominent PTH decrease in patients with a cholecalciferol deficiency. However, there are still a small proportion of patients that remain deficient, despite the high doses of cholecalciferol. In addition to the dose of cholecalciferol supplementation, this might be related to compliance of intake of the supplements. This is the most difficult point in this study because this is unfortunately difficult to control. Next to the above-mentioned factors, we need to take procedure-specific influences into account, because bariatric procedures are not all the same regarding absorption of vitamins and minerals, especially calcium and vitamin D (7, 8). Calcium is mainly absorbed in the duodenum and proximal jejunum, which is facilitated by the presence of vitamin D in an acidic environment (9). Vitamin D is absorbed in the distal jejunum and the ileum. As malabsorptive effects increase, so does the malabsorption of vitamins in specific parts of the small intestine (2). However, in this study, no significant differences in serum 25-hydroxyvitamin D, calcium, and PTH were found between the different surgical procedures.

Limitations

Only biochemical outcomes were presented in this study. The clinical outcomes were not mentioned. A larger and better-designed study including a DEXA scan is necessary to understanding the effects on calcium metabolism and bone density on long term. There is a known seasonable variability regarding (metabolites of) vitamin D, and it is therefore difficult to correct for this statistically. Furthermore, to determine clinical outcomes (osteoporosis risk and fracture incidence), a long-term follow-up is necessary. Finally, the influence of patient compliance to supplement intake was not included in this study, which could have a major influence on serum outcome measurements.

Conclusion

According to this retrospective study, a standard daily cholecalciferol supplementation regimen of 800 IU and additional cholecalciferol 50,000 IU monthly results in higher serum 25-hydroxyvitamin D and less vitamin D deficiencies. This regimen cannot treat all vitamin D deficiencies and 20% of these patients is still deficient. Therefore, this regimen needs to be further optimized and lifelong medical follow-up is necessary. A randomized clinical trial is necessary to investigate the biochemical effect of different cholecalciferol supplementation regimen including patient compliance of supplement intake after bariatric surgery.

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PART II

Assessment in patient adherence in multivitamin supplementation after bariatric and metabolic surgery

CHAPTER 8

Patient's adherence in multivitamin supplementation after bariatric surgery: a narrative review

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Abstract

Morbid obesity is a growing problem worldwide and has subsequently resulted in wide application of bariatric surgery to achieve long-term weight loss and improvement of obesity related co-morbidities. In spite of these clinical benefits, vitamin deficiencies are common after bariatric surgery and therefore, lifelong intake of a multivitamin supplement (MVS) is recommended. However, patient adherence to MVS intake is generally poor. The aim of this narrative review is to analyze which factors influence the adherence to MVS intake after bariatric surgery. To provide an extensive overview, we will discuss the different factors that influence MVS use in patients who underwent bariatric surgery, but also review the literature on MVS in other patient groups.

Introduction

Morbid obesity is a growing problem worldwide, which has led to a significant parallel growth in bariatric surgical procedures. Sleeve gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB) are currently the most common performed procedures worldwide, although more recently the One Anastomosis/Mini-Gastric Bypass (OAGB/MGB) has gained popularity (1). Bariatric surgery results in rapid weight loss and reduction of obesity related co-morbidities such as hypertension, hypercholesterolemia, diabetes mellitus type 2 and obstructive sleep apnea syndrome (2). In spite of multiple clinical benefits, bariatric surgery can lead to deficiencies in macronutrients and micronutrients as a consequence of a reduced intake, changes in eating pattern, food intolerance, gastro-intestinal symptoms and malabsorption (3, 4). This is confirmed by the recently published systematic review by Zarshenas et al. who found an unbalanced nutritional diet with inadequate protein intake and micronutrients in many included studies (5). A multivitamin supplement (MVS) is routinely recommended lifelong to prevent vitamin deficiencies (4, 6-10). However, vitamin deficiencies are quite common after bariatric surgery despite the use of a MVS, which can lead to serious long-term complications (3, 11-13). Zarshenas et al. reported about an inconsistent adherence to MVS intake after bariatric surgery (5). Many other studies have shown that long-term adherence of bariatric patients to MVS intake is poor (10, 12-18). However, it is unclear which factors contribute to patient adherence in taking MVS. Zarshenas et al. also described that further longer term and more robust studies are needed to assist healthcare professionals in providing nutritional care for bariatric surgery patients (5).

The aim of this narrative review is to analyze which factors have an influence on adherence to MVS intake after bariatric surgery, which could be complementary to the study by Zharshenas et al. Insights in determinants of behavior are therefore important if healthcare professionals want to optimize therapeutic adherence (19). To give an extensive overview, we will discuss the different factors that influence MVS use in patients who underwent bariatric surgery, but also review the literature on therapeutic adherence in other patient groups.

Methods

Pubmed and The Cochrane Library were searched from the earliest date of each database up to May 2020. The following keywords were used: bariatric surgery, metabolic surgery, multivitamin supplementation, multivitamin supplement, multivitamin intake, patient compliance, patient adherence. The following subheadings were used in this review: 1) patient related factors, 2) therapy related factors, 3) psychosocial and economic factors and 4) healthcare related factors. This classification was established by our research group based on the studies by Jin et al. and Osterberg et al. (19, 20). The terms "adherence" and "compliance" are widely used in the literature.

The term adherence is most commonly used in the world of bariatric surgery. The term "adherence" is therefore used in this review to aim for clarity. Other patient groups were analyzed as well, because the available literature on patient adherence after bariatric surgery was too limited. Therefore, it was not possible to perform a systematic review and a narrative review was chosen in which all available literature was included. Afterwards, all references of all publications were checked to not miss important publications.

Patient adherence after bariatric surgery

Patient adherence to MVS intake is a complex problem, which is largely unsolved in current bariatric practice. In general, adherence to MVS intake is poor in the long-term. A prospective analysis by Ben-Porat et al. described the prevalence of deficiencies and supplement consumption 4 years after SG (16). A significant decrease in adherence over the postoperative course was documented for MVS intake (92.6% versus 37% for 1 year and 4 years, $p = < 0.001$), vitamin D intake (71.4% versus 11.1% for 1 and 4 years, $p = < 0.001$) and calcium (40.7% versus 3.7% for 1 and 4 years, $p = 0.002$) (16). Ledoux et al. described long-term deficiencies based on adherence to a standardized MVS after RYGB (10). Non-adherence patients had more deficiencies than compliant patients (4.2 ± 1.9 versus 2.9 ± 2.0 per deficiency per patient, $p < 0.01$). The number of patients with more than 5 deficiencies was significantly higher in the non-adherence patient group ($p < 0.05$) (10). Non-adherence patients developed more vitamin deficiencies than good adherence patients (10, 16).

Bariatric surgery related factors

Postoperative complaints can cause nausea, bloating, gastro-esophageal reflux disease or dysphagia, which can lead to an inadequate food or MVS intake (21). One of the most common complaints is vomiting, occurring in 30% of patients in the first postoperative period after SG (4, 21). Several other causes have been described in the literature: food intolerance, stenosis or obstruction, marginal ulceration, internal herniation, symptomatic gallstones, medication and dumping syndrome (21). Prolonged vomiting can result in nutritional deficiencies (4). Also, diarrhea can occur due to early or late dumping syndrome, malabsorption, lactose or fructose or other food intolerances or bacterial overgrowth (4, 21, 22). Disturbed eating behavior like inadequate chewing, over distention of the pouch by fluids, large volume meals, unhealthy product choice and simultaneous eating and drinking are major factors in developing these complaints (3, 21). This implies that counseling bariatric patients prior to surgery to modify their eating behavior should be recommended.

Patient-related factors

Age and gender could be contributing factors for MVS adherence following bariatric surgery, but this impact is controversial. Particularly in adolescent bariatric patients, adherence to MVS intake appears to be low (4). One of the possible explanations is that if adolescents initially experience problems with MVS intake, they never re-initiate this behavior which could lead to a decline in adherence over time (3). Modi et al. assessed multivitamin adherence in 41 adolescents after bariatric surgery in a prospective observational study (3). In their study, no significant differences were found between baseline age and patient adherence. A prospective study by Ben Porat et al. assessed the prevalence of vitamin deficiencies and MVS consumption 4 years after SG, which show no significant differences between MVS intake and age or gender (16). A prospective cross-sectional study by Sunil et al. analyzed the relationship between vitamin adherence and demographic or psychological factors after bariatric surgery (18). Non-adherence was associated with gender (male) and employment (full-time work).

Therapy-related factors

The MVS regimen could have a major impact on patient adherence, because taking several pills every day is a problem for many bariatric patients (4). Forgetting MVS and difficulty swallowing MVS are the two primary barriers identified for all assessment points by Modi et al. (all studied assessment points were: forgetting, inconvenience, too expensive, difficult to understand doctors instruction, hard to swallow, dosing does not match my lifestyle, side effects and would rather do something else) (3). See also the section ‘patient-related factors’.
The composition of a MVS also has a major influence on the effect. Disintegration properties of the MVS are critical factors after bariatric surgery (3, 22). The solubility and surface area are compromised by malabsorptive procedures, which influence drug absorption and bioavailability. Reduction of functional gastro-intestinal capacity after bariatric surgery could lead to reduced MVS bioavailability. MVS with a long absorptive phase will have compromised dissolution and absorption. Therefore, slow-release MVS should be avoided after bariatric surgery. In addition, the solubility of MVS is affected by pH due to the decreased production of hydrochloric acid (22, 23). Literature on the disintegration properties of MVS in bariatric surgery patients is limited and should be the subject of future research (24).

Psychosocial and economic factors

It is generally accepted that psychopathological conditions and emotional support from friends and family may have an impact on clinical outcome. However, no well-designed studies have studied this impact on MVS adherence in bariatric surgery patients.
The costs of treatment with MVS have always been considered a major barrier to adequate lifelong adherence (4, 25, 26). Patients believe that the costs of specialized MVS do not weigh up to the benefits, which can lead to lower adherence (26). Homan et al. assessed the cost-effectiveness of high-dose specialized weight loss surgery (WLS) MVS and regular (‘over-the-counter’) MVS (26). In terms of costs, there is a price difference between specialized WLS MVS and regular MVS: €30 versus €21 respectively. However, patients in the regular MVS group developed significantly more vitamin deficiencies (30%) compared to the WLS MVS group (14%). Therefore, the costs for the healthcare system are significantly higher for patients that use regular MVS in case of more vitamin deficiencies due to additional

return visits and associated costs for medical staff. Total costs per patient for preventing and treating nutritional deficiencies were €306 for regular MVS and €216 for WLS MVS every 3 months. In terms of incremental costs per patient, the WLS MVS was less costly (26).

Healthcare factors

Lier et al. have performed a randomized controlled trial (RCT) in patients eligible for bariatric surgery, where a preoperative counseling group and control group without preoperative counseling were compared on patient adherence to treatment guidelines (27). Preoperative counseling consisted of improvement of coping skills to initiate and maintain postoperative lifestyle changes. Results showed no significant differences in recommended daily MVS intake (87% versus 86% for intervention and control group respectively, $p = 0.981$). Preoperative counseling did not increase MVS adherence (27). Ledoux et al. performed a long-term prospective study of nutritional deficits based on adherence to a standardized nutritional care after RYGB (10). Non-adherence patients had more vitamin deficiencies than adherence patients (4.2 ± 1.9 versus 2.9 ± 2.0 deficiencies per patient, $p < 0.01$) and the number of vitamin deficiencies correlated with the time from last visit ($r = 0.285$, $p < 0.01$). Time from last visit was significantly higher in non-adherence patients with a gap of 22 months (11.9 ± 1.5 months versus 34.1 ± 8.3 months for adherence and non-adherence patients respectively) (10).

There are no data how knowledgeable healthcare professionals are at recognizing and prescribing appropriate dosage formulations after bariatric surgery (22). The literature was searched for the influence of postoperative bariatric visits and postoperative psychological and behavioral medicine visits, but these subjects were not investigated in the bariatric patient population.

What can we learn from topics of adherence in patients with other chronic diseases?

Patient-related factors

Jin et al. performed a systematic review of 102 included articles on patient adherence in general (19). Studies with a very specific patient population were eliminated to make this review generalizable to the general patient population. In this study, age was correlated to patient adherence (19). This effect of age could be divided into three groups: the young group (< 40 years), the middle-age group (40 – 54 years) and the elderly group (> 55 years). Patient adherence in the middle-age group increased with increasing age. Overall, a higher adherence was obeserved in the elderly group (19). However, no correlation was found between adherence and age in the cross-sectional questionnaire study by Yavuz et al., which studied the influence of patient characteristics and behavior loss on patient adherence in renal transplant recipients ($p = 0.509$) (28). Contradictory, the adherence among men was lower than among women ($p = 0.087$). Patients who smoke and/or drink alcohol during the pre-and posttransplant periods are more often non-adherence ($p = 0.008$ and $p = 0.03$ for smoking and alcohol, respectively) (28).

A cross-sectional survey by Stone et al. examined the relationship between antiretroviral medication regimen complexity and patient understanding of correct regimen dosing to adherence in woman with HIV/AIDS (29). No association was found between adherence and race or ethnicity (29), which is confirmed by the review of Osterberg et al. (20). Kaplan et al. describes the opposite in a study about sociocultural characteristics that predict non-adherence with lipid-lowering medication by patients' self-assessment of medication taking practice (30). Independent predictors of non-adherence in multivariate analysis were race (OR = 3.7, $p < 0.01$), unmarried status (OR = 2.1, $p < 0.01$) and lack of insurance (OR = 2.4, $p = 0.05$) (30). The influence of education level on adherence can be considered contradictory as well: no associations were found by Stone et al. (29), while an association was found between good employment and adherence ($p = 0.01$) in the prospective telephone survey was used by Shaw et al. to analyze factors associated with non-adherence in 243 hypertensive patients who using antihypertensive medication (31). In addition, patient adherence tended to increase with educational background ($p = 0.059$) by Yavuz et al. (28). However, the review by Jinn et al. suggests that patients with lower educational levels may put more trust in the advice of healthcare professionals (19). Patients with a low income are more likely to be non-adherence (30, 32), whereas costs of medical therapy pose less of a problem if patients have a higher income (19). At the same time, adherence may be threatened if patients are not able to take time off from work for healthcare treatment (31, 33).

8

Therapy-related factors

Complexity of treatment regimen is a major predictor of poor adherence and this is inversely proportional to dosage frequency (20). Long duration of the medical treatment period may adversely affect adherence as well (34). Some studies are elaborated for illustrative purposes. Farmer et al. used prescription claim records of calcium channel blocking agents (n = 9807) to determine the mean adherence ratio over a period of 2 years (34). The mean adherence ratio was 78.2% and associated factors were the number of daily doses ($p < 0.001$) and the length of treatment regimen ($p < 0.001$). Once-daily regimen provides the highest adherence of 84.9% followed by twice-daily regimen (79.9%), three times daily regimen (75.2%) and four times daily regimen (73.1%). Once and twice daily regimens differ significantly ($p < 0.05$) (34). Claxton et al. performed a systematic review of the association between dose regimens and medication adherence and 76 studies were included (35). Mean dose-taking adherence was 75% (range 34-97%) and patient adherence decreased as the number of daily doses increased: 79% ± 14% for once-daily regimen followed by twice-daily regimen 69% ± 15%, three doses daily 65% ± 16% and four doses daily 51% ± 20% ($p < 0.001$). Significant differences in adherence were observed between 1 versus 3 doses daily ($p = 0.008$), 1 versus 4 doses daily ($p < 0.001$) and 2 versus 4 doses daily ($p = 0.001$). One versus 2 doses daily and 2 versus

3 doses daily showed no significant difference (35). Iskedjian et al. reported a high adherence rate for once-daily antihypertensive medication regimen (91.5 ± 2.2%) compared to a twice daily regimen (90.8 ± 4.7%, $p = 0.026$) and multiple daily dosing regimen (83.2 ± 3.5%, $p < 0.001$) (36). Therapeutic non-adherence is associated with poor treatment outcomes (37). For example, poor therapy adherence results in poorly controlled blood pressure which increases the risk of myocardial ischemia, stroke or renal impairment (19). Paes et al. evaluated the impact of dose frequency on adherence in patients who using oral antidiabetic agents (38). Patients received these antidiabetic drugs in a medication event monitoring system container. Each opening of the package was registered, and a questionnaire was completed at the time of the study (n = 91). Overall adherence was 74.8% with an average of 79% in one-daily doses regimen and 38% in three doses daily ($p < 0.01$). Overconsumption was occur, because one-third of this patients used more doses than prescribed (38).
Hungin et al. determined factors associated with adherence using diary cards and questionnaires in patients with chronic use of proton pump inhibitor (PPI) (n = 158) (39). Questionnaires showed a adherence rate of 70.9% taking PPI on a once-daily regimen followed by 15.8% on most days and 13.3% took them sometimes (39). Diaries showed complete adherence in 9 patients and other patients take their medicines on less than 50% of the days.

Overall, predominant barriers of non-adherence were length of treatment period (34), daily dose frequency (34-36), dose omission (36, 38), personal preference about when to take the medicine (39), fear of side effects (39) and medication knowledge (40, 41). Adverse effects of medical therapy have a major influence as these effects may cause physical discomfort and skepticism about efficacy of the prescribed medication and subsequently a lowered trust in healthcare professionals (32, 42).

Psychosocial and economic factors

Patients’ beliefs about causes and meaning of illness and motivation are strongly associated with their adherence to medical therapy (43). Adherence is better if patients feel susceptible to the illness, believe that illness or its complications pose severe consequences for patients’ health and believe that the medical therapy will be effective and beneficial (40, 44). Contrarily, erroneous beliefs or misconceptions may contribute to poor adherence and fear or negative attitude toward medical therapy is a strong predictor of poor adherence (19, 41). Gascon et al. identified factors associated with non-adherence in patients with hypertension using antihypertensive medicines (41). A qualitative study with seven focus groups was performed. Patients’ beliefs and attitude towards antihypertensive drugs and about hypertension were identified as influencing treatment adherence: fears about long-term use of medication (‘long-term use of antihypertensives is damaging’), being stuck with antihypertensive medication for life, negative feelings about the medication (‘antihypertensives are damaging’) and adverse effects. It was also noted that patients self-experimented with the antihypertensive doses, when their blood pressure was controlled ('disease is cured when my blood pressure is controlled'). In addition, many patients stop their medication to see how they feel without it, due to low awareness about treatment, risk factors and the complications of hypertension (41). Sewitch et al. prospectively identified factors of non-adherence to medication in outpatients with established inflammatory bowel disease (n = 153) (45). Non-adherence was predicted by disease activity (OR = 0.55, $p = 0.002$), disease duration ($p < 0.001$), scheduling a follow-up appointment ($p < 0.001$) and certainty that medication would be helpful ($p = 0.040$) (45). Forgetfulness (30%) was another major factor resulting in poor adherence (20).

Emotional support reduces negative behavior and attitude to therapy and improves motivation and remembering to implement the therapy (19, 43). The influence of emotional support on adherence of adolescents with chronic disease (asthma, epilepsy, rheumatoid arthritis, diabetes mellitus) was studied by Kyngas et al. in a prospective questionnaire study (n = 1061) (43). Logistic regression was used to indicate the good adherence predictors. Support from healthcare professionals, friends and family are statistically significant factors in predicting adherence. Support from nurses was the most powerful predictor (OR 7.28; 95% CI 3.95 – 13.42, $p < 0.001$) followed by support from physicians (OR 3.42; 95% CI 1.87 – 6.25, $p < 0.001$), parents (OR 2.69; 95% CI 1.42 – 5.08, $p = 0.002$) and friends (OR 2.11; 95% CI 1.28 – 3.48, $p = 0.004$), all compared to patients without support. Other interesting powerful predictors were energy and willpower to take care of themselves complied with treatment regimens (OR 6.69; 95% CI 3.91 – 11.46, $p < 0.001$) and motivation (OR 5.28; 95% CI 3.02 – 9.22, $p < 0.001$), compared to patients without energy, willpower and motivation (43).

Therapeutic non-adherence leads to an increased financial burden for society, because it is associated with more emergency care visits, hospitalizations and higher treatment costs (19, 46). Of all medication-related hospital admissions in Australia and in the USA, respectively 25% and 33-69% are due to poor medical therapy adherence (19, 20). Svarstad et al. using drug claims data of mentally ill patients to assess the association of medication adherence (neuroleptic, lithium, antidepressant) with hospitalization and costs (46). Irregularly medication use was observed in 31% of patients with schizophrenia or schizoaffective disorder, 33% in patients with bipolar disorder and 41% in patients with other severe mental illness. Irregular medication users had significant higher rates of hospitalization in all groups compared to regular users: more hospital days (16 days vs. 4 days, $p < 0.01$) and higher hospital costs ($3992 vs. $1048, $p < 0.01$) (46). In addition, psychological problems such as depression, anxiety, anger or fears about the illness are major predictors for patient adherence (19, 30).

Furthermore, medical therapy costs or co-payment were found to be associated with non-adherence as the treatment period could be life-long (19, 31, 47). Ellis et al. analyzed the influence of medicine costs on adherence in patients using statin for primary and secondary prevention (n = 4802) (47). Increasing medicine treatment costs had a large negative effect on adherence: 76.2% non-adherence with costs of $20/month vs. 49.4% non-adherence with costs of less than $10/month. Patients who payed $10 till $20/month were 1.45 times more likely to be non-adherence, compared to medicine costs less than $10/month (OR 1.45; 95%

CI 1.25 – 1.69). Patients who paid more than $20/month were 3.23 times more likely to be non-compliant, compared to medicine costs less than $10/month (OR 3.23; 95% CI 2.55 – 4.10) (47).

Healthcare factors

There are many methods available for measuring adherence, but no method is considered the gold standard. However, patient questionnaires and self-reports are described as simple, inexpensive and most useful methods in a clinical setting (20). Patient's satisfaction with clinical visits improved their medical therapy adherence (41, 42). However, lack of accessibility and availability to healthcare and long waiting time for clinic visits contributed to poor adherence (19, 33, 41, 48).

Major predictors associated with poor adherence are an inadequate follow-up or discharge planning, poor provider-patient relationship and missed appointments (44, 45, 47, 48). Spikmans et al. analyzed the reasons for non-adherence for nutritional care clinics in patients with diabetes mellitus in a cross-sectional survey study (48). One-third of these patients skipped one or more dietician visits. Non-adherence in the clinic was associated with satisfaction with the dietitian, risk perception and feelings of obligation to attend (48). Sewitch et al. reported total patient-physician discordance as predicted factor of non-adherence (p = 0.01) (45). Gascon et al. described major predictors in the patient-doctor interaction: patient-doctor interaction not encouraged, short time consultation, little time is spent regarding information, difficulty to understand doctor's language, eye contact is rarely made during consultation and clinical encounter created nervousness. In addition, information is provided mostly upon request by patient and just a few questions asked by the doctor ('there is not really any conversation, the doctor is explaining what's wrong and he doesn't even look at you') and information is too general and not tailored to patients individual ('the doctor gives you advice, but he don't tell how to practice it') (41). The overall ability of healthcare professionals to recognize patient non-adherence is poor (20).

Using a mobile phone reminder app probably could improve patient adherence of medical therapy. The effect of mobile phone text messaging for medication adherence in patients with chronic disease was described in the meta-analysis by Thakkar et al. (49). Sixteen randomized clinical trials with a total of 2742 patients were included (5 of personalization, 8 using two-way communication and 8 using a daily text message frequency). Text messaging significantly improved medication adherence from 50% to 67.8%, which is promising. The authors advise to interpret the results carefully, due to the short follow-up and reliance on self-reported medication adherence measurements. Ramsey et al. published a pilot investigation of a mobile phone application and progressive reminder system to improve medication adherence in 35 patients with migraine (50). Medication adherence was significantly improved in older patients with a lower baseline adherence during the first month of this study. Self-reported app-based adherence rates were significant lower when compared to electronically monitored adherence rates. Future research needs to examine the effect of features of mobile phone message or reminder apps, appropriate patient populations, the influence on clinical outcomes and sustained long-term effects (49, 50). Table 1 gives an overview of the described barriers that influence patient adherence in bariatric surgery patients and other patient populations.

Discussion

The long-term adherence to MVS intake after bariatric surgery is often poor and underlying factors are unclear. This narrative review analyzed which factors have an influence on adherence to MVS intake after bariatric surgery. Although data on the influence of demographic characteristics are limited and contradictory, many potential causes for poor MVS adherence in bariatric patients have been identified (3, 4, 16, 18). Among these the most important are: eating behavior (3, 21), postoperative complications leading to gastro-intestinal symptoms (4, 21, 22), treatment complexity (daily pill frequency) (4), composition of MVS (3, 22, 23) and costs of MVS treatment (4, 25, 26). Another important topic is that patients often believe that the costs of specialized MVS do not weight up to the benefits, which can lead to lower adherence (26).

Table 1: Factors that influence patient adherence in bariatric patients and other patient populations

	Bariatric patients	Other patient groups
Patient-related factors	Age Gender Employment Postoperative complications Postoperative complaints Eating behavior	Age Education levels Employment and income
Therapy-related factors	Forgetting Swallowing Disintegration properties of MVS	Duration of the medical treatment Frequency of dose Convenient way of administration Adverse effects of medication
Psychosocial and economic factors	Costs of MVS treatment	Patients lack belief in benefit of treatment Erroneous beliefs or misconception Negative attitude toward medication Treatment of asymptomatic disease Presence of psychological problems Forgetfulness or other priorities Emotional support Costs of medical therapy
Healthcare-related factors	Yearly medical visits	Satisfaction with clinical visits Inadequate follow-up due to missing appointments Discharge planning Poor patient-doctor relationship Mobile phone message or reminder apps

MVS: multivitamin supplement

However, the available literature on the influence of these topics in bariatric surgery patients is limited. Knowledge gained from studies in other patient populations may therefore be useful for increasing long-term adherence. Major therapy-related factors are described more extensive in other patient populations. Complexity of treatment is a major predictor of poor adherence and this is inversely proportional to dosage frequency and have been studied in many different patient populations, as well as duration of medication treatment, side effects and medication knowledge (20, 34-36, 38-41). Absence of disease symptoms worsened patient adherence (41). Patients lack of belief in benefit of treatment, have erroneous beliefs or experience misconception. Therefore, negative attitudes toward medication may have negative effects on patient adherence (41, 43). The absence of emotional support, low satisfaction with clinical visits, inadequate follow-up due to missing appointments, discharge planning and a poor patient-doctor relationship are studied in many different patient groups and are associated with poor adherence (19, 20, 33, 41-45, 47, 48). Perhaps the most challenging objective for healthcare professionals is to have their patients compliant to the lifelong use of medical therapy. Early recognition and intervention may improve patient adherence. Overall, the ability of healthcare professionals to recognize patient non-adherence is poor (20). They contribute to poor adherence by failing to explain the benefits and side effects, by prescribing complex medical therapy regimens, not giving consideration to a patient's lifestyle or the costs of the treatment and having a poor therapeutic relationship with their patients as the most important factor (20). Not knowing patients' priorities may have a high potential for low adherence (41). However, the doctor-patient interaction on MVS adherence in bariatric patients remains poorly understood. Our hypothesis is that patients want to please the doctor due to the discrepancy between what the patient tells and what the patient actually does. This emphasizes the importance of a good doctor-patient relationship. When a patient's condition or illness is not responding to MVS, poor adherence should always be considered. One of the factors that leads to lower adherence is the belief patients have that the costs of specialized MVS do not weigh up to its benefits. Therefore, healthcare professionals should pay attention to explain the benefits and side effects when prescribing complex MVS regimens, hereby given consideration to a patient's lifestyle and the costs of treatment. Patients' perceptions and their personal and social circumstances are crucial to their decision-making. An irrational act of non-adherence from the doctor's point of view may be a very rational action from the patient's point of view. Thus the solution lies not in attempting to increase patient adherence, but in the development of a more open, co-operative doctor-patient relationship (51). Enhancing communication between healthcare professionals and patients is an effective strategy boosting the patient's ability to follow a medication therapy regimen (20). Other important issues are the daily dose regimen in bariatric patients and the prescription of supplements in the absence of symptoms. Bariatric patients often use 3 or 4 vitamin tablets daily, while literature in other patient populations shows that a simple regimen with one pill once a day helps to maximize adherence (20, 36). Gastro-intestinal symptoms or incorrect eating techniques probably play a very important role in taking MVS after bariatric surgery, while patients often think that these symptoms are caused by the MVS. However, this remains the subject of further studies. Another contributing factor is a significant postoperative change in taste following bariatric surgery such as a decrease in intensity of taste, aversion to certain food types (52).

But the most important factor is a proper formulation of the supplements, which requires consideration of the biological, physical and chemical characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product (53). Pharmaceutical and drug materials utilized must be compatible. Successful development of a formulation includes multiple considerations involving the drug, storage, packaging, stability and excipients. The proper combination of taste, appearance, flavor and color in a pharmaceutical product contributes to its acceptance and a better adherence (53). However, these important pharmaceutical points are not studied in the bariatric patient population.
Limitations of this narrative review are the limited results of patient adherence to MVS intake after bariatric surgery. Overall, a poor adherence to MVS intake is described, and this topic is described in almost every publication about vitamin deficiencies after bariatric surgery. However, it remains only at percentages. Only a few studies described a limited number of factors that can affect this adherence. There is insufficient information available therefore, to perform a systematic review about this subject.

Recommendations for future research

A cross-sectional study after bariatric surgery is recommended to analyze the different barriers responsible for poor MVS adherence. Besides studying specific patient groups, it is advised to involve various healthcare professionals to educate patients on the nutritional consequences of their obesity treatment. A multidisciplinary approach, facilitating the expertise from all specialties involved in bariatric care should also include a role for the general practitioner to improve long-term adherence.

Conclusion

Long-term adherence to MVS intake after bariatric surgery is often poor, and there is only limited data on the different factors that influence MVS adherence in bariatric patients. These factors are limited to patient-related factors (age, gender, employment), bariatric surgery related factors (postoperative complications, gastro-intestinal complaints and eating behavior), therapy-related factors (side effects and composition of MVS), economic factors (costs of MVS) and health-care related factors (yearly medical visits). A cross-sectional study after bariatric surgery is recommended to analyze the different barriers responsible for poor adherence to MVS intake. Knowledge gained from studies in other patient populations may therefore be useful for increasing long-term adherence. Patient-centered education is the cornerstone in achieving higher adherence rates, which emphasizes the need for dedicated bariatric teams, including dietitians and mental health professionals, and also has an important role for the general practitioner.

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CHAPTER 9

Factors affecting patient adherence to multivitamin intake after bariatric surgery: a multicenter survey study from patient's perspective

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Abstract

Background

Lifelong multivitamin supplementation is recommended to prevent nutritional deficiencies. Despite this advice, deficiencies are common which may be due to poor adherence to multivitamin supplement (MVS) intake. The aim of this study was to identify which factors affect patient adherence to MVS intake after bariatric surgery.

Materials and Methods

A 42-item questionnaire was sent to 15,424 patients from four Dutch bariatric centers. In total, 4975 patients wanted to participate of which 361 patients were excluded. A total of 4614 patients were included, and MVS users (n = 4274, 92.6%) were compared to non-users (n = 340, 7.4%). Most patients underwent Roux-en-Y gastric bypass (64.3%) or sleeve gastrectomy (32.3%).

Results

Seven hundred and ten patients (15.4%) reported inconsistent MVS use and 340 patients (7.4%) did not use any MVS at all. For inconsistent MVS users, most reported reasons included forgetting daily intake (68.3%), gastro-intestinal side effects (25.6%) and unpleasant taste or smell (22.7%), whereas for non-users gastro-intestinal side effects (58.5%), high costs (13.5%) and the absence of vitamin deficiencies (20.9%) were most frequently reported. Overall, 28.5% were dissatisfied about instructions on MVS use, attention paid to MVS use during medical consultation and the extent to which personal preferences were taken into account.

Conclusion

The attitude of bariatric patients towards MVS use is predominantly negative. It is important to provide accurate information on different options for MVS intake and collect information about patient’s personal preferences when prescribing supplements. Improving adherence to MVS intake is challenging and requires implementation of a shared decision-making process, further optimization of MVS formulas and exploring options for reimbursement.

Introduction

Worldwide, morbid obesity is a fast-growing problem for which bariatric surgery is an effective treatment to lose weight and improve obesity related comorbidities including hypertension, dyslipidemia, type 2 diabetes mellitus and obstructive sleep apnea syndrome (1). In spite of multiple clinical benefits, all bariatric procedures, to variable degrees, alter the anatomy and physiology of the gastro-intestinal tract. As a result, patients are more susceptible to developing nutritional deficiencies. Therefore, lifelong use of a multivitamin supplement (MVS) is recommended (2-4). However, therapeutic non-adherence to MVS intake after bariatric surgery is frequently encountered in both clinical practice and research and is therefore a major topic of discussion (5, 6). Despite proven safety and effectiveness, a large number of bariatric patients stop taking MVS or become less consistent with MVS intake over time. Potential barriers and facilitators of non-adherence have recently been described in a narrative review by our study group (7), but research in the population of bariatric patients is lacking. The aim of this study is to identify which factors affect patient adherence to MVS intake after bariatric surgery from a patient perspective.

Materials and Methods

We conducted a cross-sectional non-validated 42-question survey among bariatric patients from four high-volume bariatric centers in the Netherlands: Catharina Hospital Eindhoven, Rijnstate Arnhem, Franciscus Gasthuis & Vlietland Rotterdam and Onze Lieve Vrouwe Gasthuis. All questions were multiple-choice and divided into four topics: patient-related factors, MVS-related factors, psychosocial and economic-related factors and healthcare-related factors. The format of these topics was established based on the study by Jin et al. (8). A previous review by our research group on potential influencing factors that negatively influence the adherence to MVS intake, was used as input for the questions (7). We included patients who underwent bariatric surgery from 2010 to 2020, including sleeve gastrectomy (SG), Roux-en-Y Gastric Bypass (RYGB), one anastomosis gastric bypass (OAGB), single anastomosis duodenal-ileal bypass (SADI) and duodenal switch (DS). Patients who underwent revisional and/or secondary surgery were also included. Exclusion criteria were incomplete questionnaires and reversal of the bariatric procedure ('undo surgery'). In total, 15,424 patients were recruited between October and December 2020 (Figure 1). All data were collected anonymously in Data Management® (Cloud9, Research Manager, Deventer). Digital informed consent was obtained from all participants.

Statistical analyses

Continuous data is presented as mean ± standard deviation (SD) for normally distributed data and as median and interquartile range (Q1-Q3) for non-normally distributed data. Categorical variables are presented as frequency and percentages. Differences in outcomes between MVS users and non-users are compared using independent t-tests or Mann-Whitney U tests for continuous variables. Chi-square tests are used for categorical variables. P-values of $p < 0.05$ were considered statistically significant. Statistical Package for Social Sciences (SPSS, Chicago, IL, USA Version 25.0) was used for all statistical analyses.

Results

In total, 5239 patients (34%) signed the informed consent of which 4614 patients were available for analysis (Figure 1). The study population was divided into two groups: MVS users (n = 4274, 92.6%) and non-users (n = 340, 7.4%) (Table 1). Both groups were similar with respect to gender, educational level, body weight and body mass index. In comparison to MVS users, non-users were younger [51.0 (43.0–57.0) vs 43.0 (33.0–53.0) years] and differed in marital status, type of surgery and time since surgery ($p < 0.001$ for all). The majority of MVS users underwent RYGB (66.0%) whereas the majority of the non-users underwent SG (54.4%).

MVS-related factors

In total, 4274 patients (92.6%) used a MVS after bariatric surgery. A majority of the MVS users (85.2%) use specifically designed WLS (weight loss surgery) MVS, of which the majority used the formulations of FitForMe (69.5%). Other reported WLS formulations were “Vitamine op recept” (8.5%), Flindall (3.9%) and Elan (3.0%). A small part of the MVS users (12.7%) used regular (‘over the counter’) MVS.

Of all MVS users, 15.4% did not take their MVS consistently, for which most frequently reported reasons were ‘forgetting daily intake’ (68.3%), ‘gastro-intestinal side effects’ (dyspepsia, difficultly with swallowing, 25.6%) and ‘unpleasant taste or smell’ (22.7%). Moreover, 17.0% reported that scheduling their daily intake is difficult because of interactions with the calcium/vitamin D supplement or other medication. They believe that their MVS intake would improve if they could take all tablets at the same time. There was also a group of patients who reported not to use any MVS (n = 340). The majority of the non-users (52.7%) stopped taking MVS more than 1 year after surgery. Compared to MVS users with inconsistent MVS intake, non-users reported different reasons for discontinuing MVS intake (Figure 2). For non-users, gastro-intestinal side effects of MVS were a major factor (58.5%), as well as high costs (13.5%). A large part of the non-users also believed they did not require any MVS as their laboratory results are good and they feel physically fit (20.9%). In both groups, a small part of patients reduced or stopped MVS intake on advice of their specialist due to excessive serum vitamin.

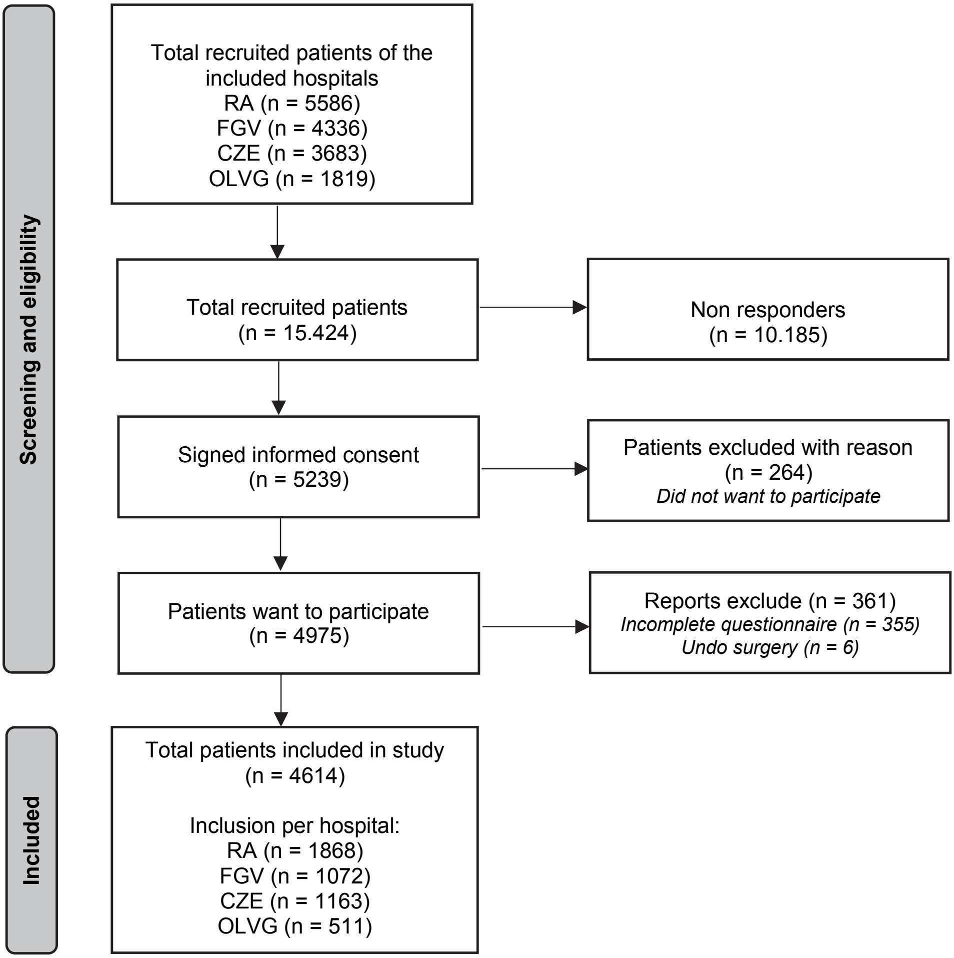


Figure 1. Flowchart patient inclusion

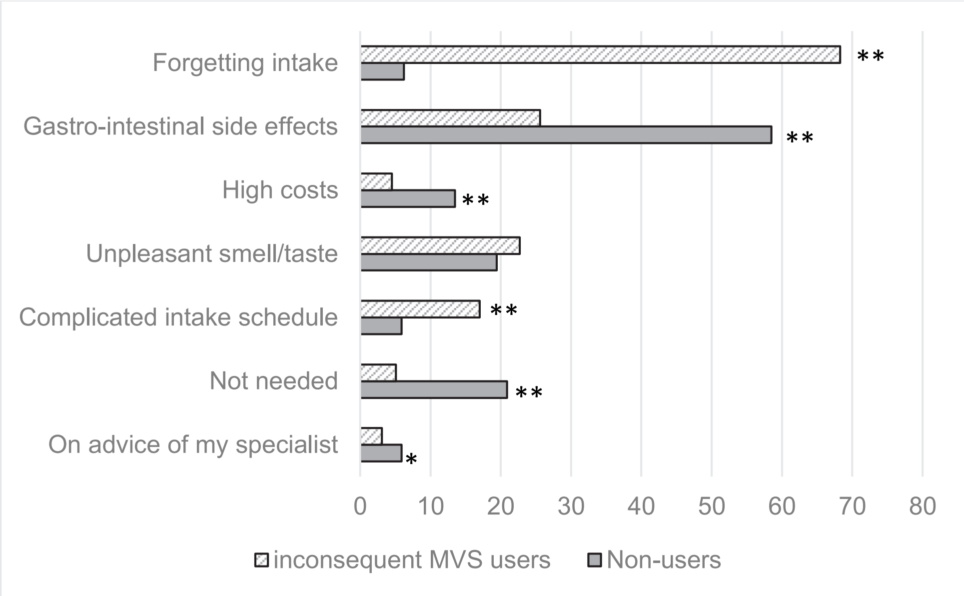
CZE: Catharina ziekenhuis Eindhoven, FGV: Franciscus Gasthuis & Vlietland, OLVG Onze Lieve Vrouwe Gasthuis, RA: Rijnstate Arnhem

Table 1: General characteristics of the study population

	Total group (n = 4614)	MVS users (n = 4274)	Non-users (n = 340)	*P*-value
Age (years)	51.0 (43.0 – 57.0)	51.0 (43.0 – 57.0)	43.0 (33.0 – 53.0)	***< 0.001*** [1]
Gender (male)	930 (20.2)	871 (20.4)	59 (17.4)	0.181 [2]
Marital status				***0.001*** [2]
- Single	772 (16.7)	694 (16.2)	78 (22.9)	
- Living with partner	606 (13.1)	547 (12.8)	59 (17.4)	
- Married or registered partnership	2900 (62.9)	2721 (63.7)	179 (52.6)	
- Divorced or separated	251 (5.4)	233 (5.5)	18 (5.3)	
- Widowed	85 (1.8)	79 (1.8)	6 (1.8)	
Education level				0.624 [2]
- Low	1165 (25.2)	1085 (25.4)	80 (23.5)	
- Middle	2062 (44.7)	1902 (44.5)	160 (47.1)	
- High	1387 (30.1)	1287 (30.1)	100 (29.4)	
Body weight (kg)	84.0 (73.6 – 97.0)	84.0 (73.5 – 97.0)	85.0 (74.1 – 98.8)	0.257 [1]
BMI (kg/m^2)	28.7 (25.7 – 32.4)	28.7 (25.7 – 32.4)	28.7 (25.9 – 33.2)	0.472 [1]
Type of surgery				***< 0.001*** [2]
- Sleeve gastrectomy	1490 (32.3)	1305 (30.5)	185 (54.4)	
- Roux-en-Y gastric bypass	2966 (64.3)	2819 (66.0)	147 (43.2)	
- One-anastomosis gastric bypass	108 (2.3)	105 (2.5)	3 (0.9)	
- Other	43 (0.9)	39 (0.9)	4 (1.2)	
- Unknown	7 (0.2)	6 (0.1)	1 (0.3)	
Time since surgery				***<0.001*** [2]
- 0-1 years	680 (14.7)	658 (15.4)	22 (6.5)	
- 1-2 years	1071 (23.2)	1024 (24.0)	47 (13.8)	
- 2-3 years	1096 (23.8)	1011 (23.7)	85 (25.0)	
- 3-4 years	866 (18.8)	771 (18.0)	95 (27.9)	
- 4-5 years	570 (12.4)	521 (12.2)	49 (14.4)	
- > 5 years	331 (7.2)	289 (6.8)	42 (12.4)	

Data are presented as median (Q1 – Q3) and frequencies (percentages)
1 Mann-Whitney U Test
2 Pearson Chi-Square Test
BMI: body mass index, MVS: multivitamin supplementation

Figure 2: Reasons for non-compliance with MVS (%)



MVS: multivitamin supplementation
* = p < 0.05, ** = p < 0.001 (Pearson Chi-Square Test)

Gastro-intestinal complaints

In this paragraph, a distinction is made between postoperative gastro-intestinal complaints in general (independent of MVS intake) and those directly related to MVS intake. General postoperative gastro-intestinal complaints (independent of MVS intake) occurred more often in non-users than in MVS users (37.4% vs. 26.3%, p < 0.001) (Figure 3a). Most reported complaints were nausea, vomiting, difficultly with swallowing, abdominal bloating, (abdominal) pain or stomach cramps and dumping. Less frequent reported complaints were diarrhea, gastro-esophageal reflux disease, belching and hiccups. The distribution of the frequency of complaints was significantly different between both groups (Figure 3b). Most non-users experienced these complaints daily while this was a few days per week or month for most MVS users (p = 0.040). Gastro-intestinal complaints that are directly related to MVS intake were reported by 58.5% of the non-users. Most frequently reported complaints were nausea (85.4%), excessive belching and hiccups (43.7%), vomiting (42.7%), difficulty with swallowing (40.2%), bloated feeling (21.1%) and reflux (18.1%). These complaints occurred immediately after ingestion (29.4%), 5-10 minutes after ingestion (43.8%), 15-30 minutes after ingestion (18.6%) or ≥ 1 hour after ingestion (5.2%). For the majority, these complaints have arisen directly after starting MVS use (72.7%). After cessation of MVS intake, 61.9% was free of complaints, while complaints reduced in 12.9% and worsened in 4.1%. In 17.0%, no differences were observed.

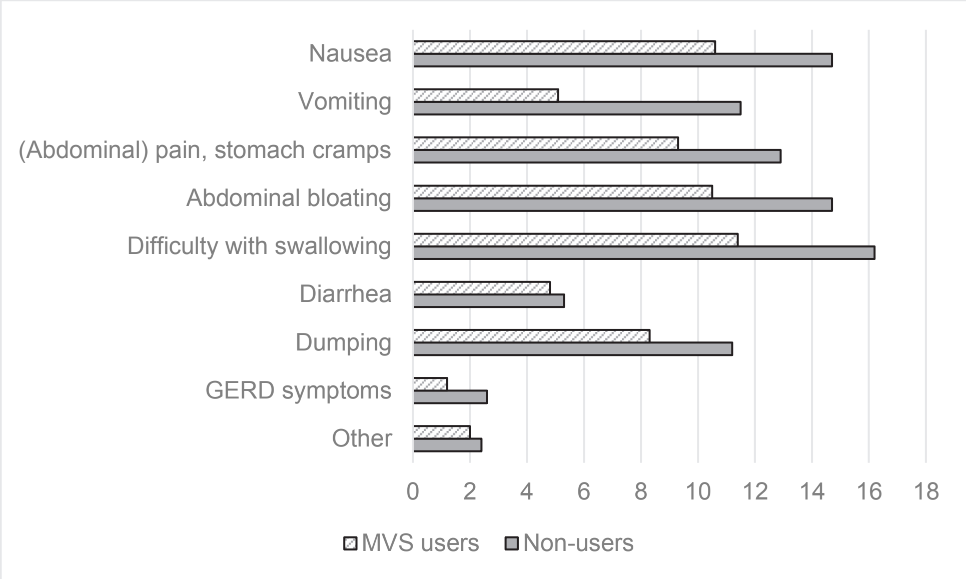


Figure 3a: Postprandial complaints of MVS users and non-users (%)*

MVS: multivitamin supplementation, GERD: gastroesophageal reflux disease
* Multiple answers possible

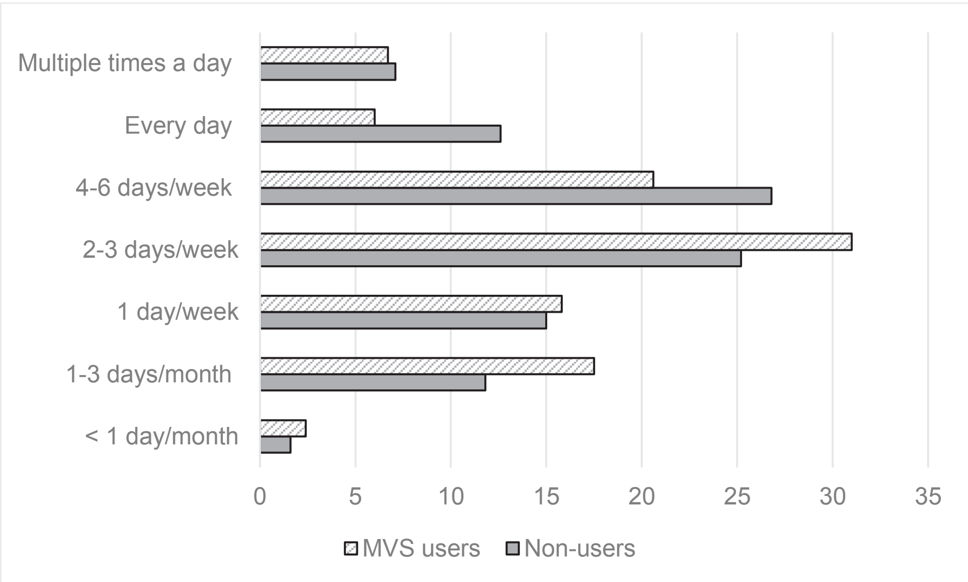


Figure 3b: Frequency of postprandial complaints of MVS users and non-users (%)

MVS: multivitamin supplementation

Psychosocial and economic factors

Differences in psychosocial-related factors are described in Table 2. Of the MVS users, 10.6% of the patients were not motivated for daily MVS intake compared to 69.1% of the non-users ($p < 0.001$). Reasons for poor motivation were absence of deficiencies (15.9%), absence of complaints (20.8%) or a combination of both (32.4%). Other reported factors included experiencing gastro-intestinal complaints directly related to MVS use (10.4%) and the unpleasant smell, taste and/or size (2.9%). Some patients forget to take their daily MVS and some patients only take their MVS because the healthcare professional tells them they have to.

Less frequent reasons are the costs of MVS and the occurrence of excessive serum vitamin A or B6. Moreover, some patients believed that they receive plenty of vitamins from their nutrition and therefore do not need to use MVS. A quarter of the non-users believe that the risk of vitamin deficiencies cannot be reduced by using MVS, compared to 9.1% of the MVS-users ($p < 0.001$). The lifelong aspect of daily intake of MVS is also a barrier for many patients (38.0% vs. 60.6% for MVS-users vs. non-users, $p < 0.001$). A majority of these patients think that their adherence would be better if the treatment period was shorter (40.3% vs. 64.6%, for MVS-users vs. non-users, $p < 0.001$). Similar to the reported reasons for demotivation, expected disadvantages from MVS use also include the high costs (17.0%), unpleasant side effects (12.2%), and risk of excessive serum levels (7.9%). Strikingly, 72.3% of the MVS users report no disadvantages of MVS use compared to 39.1% of the non-users ($p < 0.001$). Most of the MVS users think that the price is acceptable (60.6%), whereas most non-users find the costs too high (61.2%) ($p < 0.001$). Many patients indicate that reimbursement of supplements would improve their adherence to MVS intake (38.1% vs. 43.5% for MVS-users vs. non-users, $p = 0.049$).

Non-users are more often dissatisfied about the achieved postoperative weight loss compared to MVS-users (32.9% vs. 21.0%, $p < 0.001$) and 14.7% believe that MVS use has influenced their postoperative weight loss (15.2% vs. 7.4% for MVS users vs. non-users, $p < 0.001$). Similarly, more non-users reported to receive no emotional support for lifestyle changes after bariatric surgery compared to MVS-users (30.9% vs. 18.3%, $p < 0.001$). However, the majority of patients (79.0%) reported that their MVS intake is not better because of this emotional support (78.0% vs 92.8% for MVS-users vs. non-users, $p < 0.001$).

Healthcare-related factors

Non-users were more often dissatisfied about instructions provided about the importance of MVS use, attention paid to MVS use during medical consultation and the extent to which personal preferences of MVS use are taken into account, compared to MVS users ($p < 0.001$ for all, Figure 4). Most frequent reasons for scoring poorly or inadequate on one of these subscales (n = 1315, 28.5%) were 'too general information' (57.1%), 'personal preferences not taken into account' (51.0%) and 'not enough time for adequate information about MVS during medical consultations' (36.5%). Other reasons were that the patient needs to actively ask for information by themselves (28.9%) and too short consultation time (23.5%). Less frequently reported reasons were that the patient is only told what he/she is doing wrong (9.4%), they only advise one MVS formulation and do not provide alternatives (6.5%), the patient does not feel understood (5.1%) and other reasons (Covid-19 virus, topic of MVS is not discussed or 'I don't understand the doctor', 16.7%).

Table 2: Differences in psychosocial-related factors

	MVS users (n = 4274)	Non-users (n = 340)	*P*-value
Are you motivated to take MVS daily lifelong?			***< 0.001***[1]
- Yes	3819 (89.4)	105 (30.9%)	
- No	455 (10.6)	235 (69.1%)	
Why are you not motivated?			
- Good blood tests and no complaints	136 (29.8)	88 (37.4)	
- No complaints	104 (22.8)	40 (17.0)	
- Good blood tests	72 (15.8)	38 (16.2)	
- Gastro-intestinal complaints after MVS ingestion	47 (10.3)	25 (10.6)	
- Unpleasant smell/taste/size	11 (2.4)	9 (3.8)	
- Other	86 (18.9)	35 (14.9)	
Do you know why it is important to take MVS for life long*?			
- To prevent vitamin deficiencies	4058 (94.9)	300 (88.2)	-
- To feel fit and energetic	1894 (44.3)	159 (46.8)	
- To strengthen the immune system	1821 (42.6)	131 (38.5)	
- To lose more weight	34 (0.8)	8 (2.4)	
- Because the obesity center tells me that I have to take them	200 (4.7)	38 (11.2)	
- I don't know	41 (1.0)	16 (4.7)	
What disadvantages do you expect from the MVS?*			
- None	3088 (72.3)	133 (39.1)	**-**
- Unpleasant side effects	443 (10.4)	120 (35.3)	
- The (high) costs of MVS	719 (16.8)	66 (19.4)	
- Excessive serum levels	331 (7.7)	32 (9.4)	
- It has no effect	138 (3.2)	44 (12.9)	
- The physician has shares in MVS	66 (1.5)	9 (2.6)	
- Lower weight loss	58 (1.4)	4 (1.2)	
- Other	50 (1.2)	8 (2.4)	
Do you receive emotional support for lifestyle changes after surgery*?			
- No	782 (18.3)	105 (30.9)	
- Yes, from my partner	2463 (57.6)	171 (50.3)	
- Yes, from family	2247 (52.6)	161 (47.4)	
- Yes, from friends	1618 (37.9)	98 (28.8)	
- Yes, from the healthcare professionals of the obesity center	1333 (31.2)	58 (17.1)	
Is your MVS intake better because of emotional support?			***< 0.001***[1]
- Yes	767 (22.0)	17 (7.2)	
- No	2725 (78.0)	218 (92.8)	

Data are presented as frequencies (percentages)
[1] Pearson Chi-Square Test
* = multiple answers were possible
MVS: multivitamin supplement

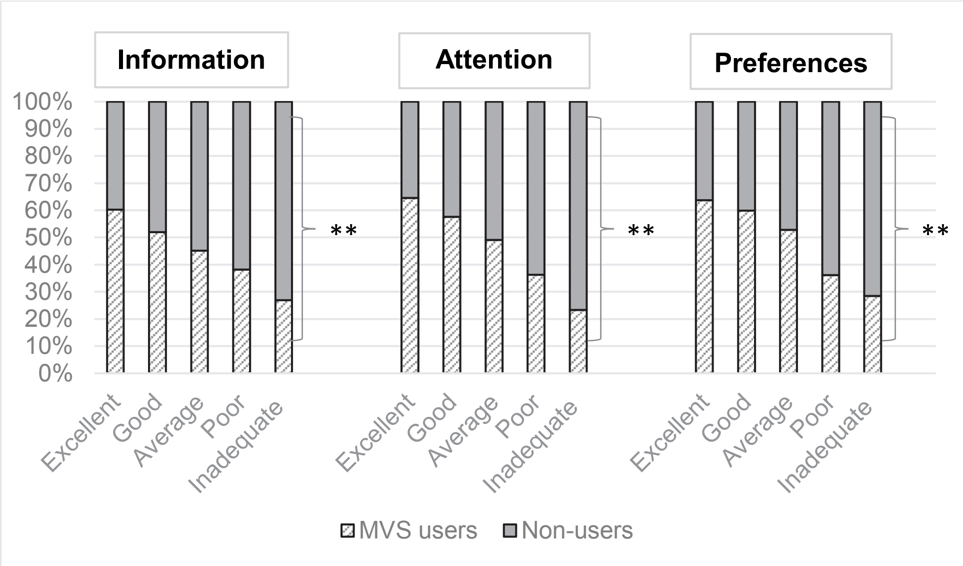


Figure 4: Rating scores of healthcare-related factors (p < 0.001, Pearson Chi-Square Test)**
MVS: multivitamin supplement

Reported unclear topics were missing information about side effects (17.8%), disadvantages (12.2%) and benefits (4.9%). Moreover, patients reported that they do not know when (6.8%) or how (4.1%) to take their MVS. Some experienced a lack of information about alternative MVS options and what to do in case of complaints (3.0%). Half of all included patients reported that their healthcare professional does not ask about MVS related complaints (50.6% vs. 42.4% for MVS users and non-users, $p < 0.001$).

Discussion

Overall, adherence to MVS therapy is poor in 22.3% of all included patients, of which one third did not use any MVS. This non-adherence rate is similar to the review by Zarshenas et al. (20-32%) (9, 10). An important difference between the MVS users and non-users in this study is the time since surgery, which was shorter for MVS users. In the study by Ben-Porat et al., 92.6% of the patients took MVS during the first postoperative year, while only 37.0% took MVS after 4 years (11). It is plausible that adherence to MVS intake is better in the first postoperative year due to an intensive follow-up, compared to multiple years after surgery when most patients are no longer supervised. The number of compliant MVS users in our study could therefore be overestimated. However, irrespective of adherence to MVS intake, the attitude of many bariatric patients towards MVS use is predominantly negative.

Barriers influencing adherence to MVS intake

Most frequently reported reasons to stop taking MVS (consistently) are gastro-intestinal complaints, high costs and an unpleasant smell, taste or size.

About one third of the patients suffered from gastro-intestinal complaints and half of the patients indicated that healthcare professionals do not discuss these complaints during medical consultations, letting this problem underexposed. A large part of the non-users believe that they do not need to take any MVS because their laboratory results are good and they feel fit. The majority of patients understand that MVS is necessary, but not everyone seems convinced of the advantages of WLS MVS. Patients often believe that the costs of WLS MVS do not outweigh the benefits, which can lead to lower adherence. However, it has been shown by Homan et al. that adequate supplementation results in less vitamin deficiencies and reduces overall healthcare costs (12). Total costs per patient for prevention and treatment of vitamin deficiencies were €306 (regular MVS users) vs. €216 (WLS users) every 3 months, with a chance of developing a vitamin deficiency of 30% (regular MVS) vs. 14% (WLS MVS) (12).

Dissatisfaction with medical consultations is another striking topic of this survey study. A third of the patients in our study was dissatisfied with the explanation about and awareness for MVS use. Many patients indicated that the information on MVS use is too general and limited and that their personal preferences were not taken into account. Healthcare professionals often recommend one type of WLS supplement and patients therefore cannot choose which supplement suits their preferences. All of these issues may consequently contribute to poor motivation for adequate MVS intake. The study by Osterberg et al. described that healthcare professionals contribute to patients' poor adherence by prescribing complex medication regimens, failing to explain side effects and benefits, not giving consideration to patient's lifestyle or the attributed costs of MVS, which may lead to a poor relationship with their patients (13). In addition, the overall ability of healthcare professionals to recognise patient's non-adherence is poor (13). These findings are confirmed by our study as many patients indicated to have a lack of proper information. These healthcare-related findings are quite similar to those found in long-term adherence studies with other chronic diseases (7).

Challenges to improve adherence to MVS intake

There are three different parties who can improve patient adherence to MVS intake after bariatric surgery. First, the healthcare professionals play a large part in improving satisfaction and patient adherence to MVS intake. We need to engage to provide better education on MVS use and better shared decision making with patients after bariatric surgery. Explanation about the necessity of MVS after bariatric surgery is an essential point, but the MVS advice by healthcare professionals is often not in line with patients' personal preferences. There are several options for using MVS, all with pros and cons, which therefore should always be discussed during consultations to increase patient satisfaction.

In addition, gastro-intestinal symptoms in general or related to MVS intake should also be part of the medical consultation in order to improve patient adherence to MVS intake. Assessment, prevention and management of gastro-intestinal complaints are an important part of postoperative bariatric care, which is described in the study by Zarshenas et al. (10). Besides that, there should be more focus on improving the relationship between patient and healthcare professional. Having knowledge of patients' perceptions, beliefs and their personal circumstances are crucial for a decision-making process. It needs to be taken into account that the preferences of bariatric patients may differ considerably from those of the healthcare professional. Thus, the solution lies in shared decision making (SDM) (14). SDM describes the process where the patient must be well informed, and patients' preferences must become a more important part during medical consultations. The emphasis is not on the final decision but on the process that works towards this decision. Several studies show that SDM has a positive effect on the interaction between patient and healthcare professional. It increases patient's level of knowledge, which leads to more accurate risk assessment of treatment options and increases patient's assertiveness during SDM (15-20). Application of SDM in MVS use after bariatric surgery could therefore be a breakthrough in improving the adherence.

Second, the MVS producers can increase therapy adherence by further optimizing their supplements. MVS formulas should be scrutinized due to the high percentage of gastro-intestinal side effects and an unpleasant taste and smell, which is indicated as an important barrier by many patients in our study. A significant decrease in intensity of taste and aversion to certain food types after bariatric surgery could be a contributing factor (21). For this reason, many patients switch from WLS MVS to regular MVS. Many regular MVS have an enteric coating, which may reduce the unpleasant aftertaste that many patients suffered from. However, this type of coating is not desirable as the ability to absorb MVS is compromised after bariatric surgery (22). A proper formula of supplements is necessary to ensure adequate absorption, which requires considerations of all drug substances and pharmaceutical ingredients (23). An ideal combination of taste, appearance and colour in supplements will contribute to its acceptance (24). MVS manufacturers must investigate how these aspects can be improved while simultaneously ensuring adequate absorption.

Third, insurance companies could contribute to the improvement of patient adherence to MVS intake by reimbursing supplements. Costs are a frequently reported reason for patients to stop using specialised WLS MVS. Reimbursement of supplements with proven effectiveness could improve the therapy adherence, which is indicated by many patients in our study. Therefore, healthcare authorities involved in the reimbursement of bariatric procedures should consider integrating costs of WLS MVS with post-operative follow-up. We believe that only reimbursing WLS MVS with proven effectiveness, based on extensive scientific research, should be considered. This reimbursement will motivate many patients to switch to WLS MVS.

Strengths
All consecutive postoperative patients were recruited to avoid selection bias. Participation was anonymous; no information from the electronic patient file was retrieved. There was no risk or personal benefit, which reduced the risk of giving socially desirable answers. To provide accurate assessment of vitamin intake, the questions were designed with a free text field option to avoid too limited answers possibilities. Because patients from four hospitals were included, the external validity of this study is high and results can be used by many (inter)national obesity centers.

Limitations
A total of 10,810 patients (70.1%) did not participate. It is unclear whether these patients use a MVS. Long-term follow-up after bariatric surgery is poor despite clear international guidelines (25). No validated questionnaire was used, as such a questionnaire does not exist. However, our survey study was intended to get a first impression of factors influencing adherence to MVS intake and analyze various topics for advice in daily practice. A validated questionnaire was therefore not required. This questionnaire contained only self-reported patient data and provides subjective information who cannot be verified due to the anonymous character, which can cause underestimation or overestimation.

Future perspectives
These results can be used for further hypothesis-generating research and perform research into the influence of different bariatric procedures (primary vs. revision surgery) and time after surgery on patient adherence to MVS intake. It is important to analyze which patient groups are at higher risk for poor adherence to MVS intake whether the percentage vitamin deficiencies is higher in patients who do not use any MVS. The relationship between patient and healthcare professional and discrepancies between experiences from both perspectives are also important topics for further clarification. Finally, the development of tools supporting SDM in MVS choices is important as well.

Conclusion

The attitude of many bariatric patients towards MVS use is predominantly negative. A large proportion of patients are dissatisfied about the advices on MVS intake during medical consultations and that patients' personal preferences are often not taken into account. High costs, no reimbursement and gastro-intestinal complaints lead to poor motivation for MVS intake. Gastro-intestinal side effects, good laboratory results and an unpleasant taste and smell are the most frequently reported reasons for the discontinuation of MVS intake. It is important to take patient's preferences into account and to provide more extensive information about different possibilities in MVS use. Challenges lie in improving patient adherence by implementing SDM in MVS use, further optimization of WLS MVS formulas and exploring options for reimbursement, which could be major factors in reducing vitamin deficiencies following bariatric surgery.

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CHAPTER 10

General discussion, conclusion and future perspectives

GENERAL DISCUSSION

Bariatric and metabolic surgery leads to significant weight loss and improvement of comorbidities (1). Vitamin deficiencies affect the majority of patients and can be considered as the most common problem after bariatric and metabolic surgery. Long-term prevention, detection and treatment of vitamin deficiencies is therefore one of the cornerstones of obesity treatment (2, 3). The aim of this thesis was to discuss several aspects in the management of vitamin deficiencies following bariatric surgery. The findings of the studies in this thesis are applicable to daily practice and can be used as clinical recommendations and tools to improve current bariatric care. The following section includes discussion points and future perspectives for the postoperative bariatric care pathway.

Part I: Nutritional and functional assessment in bariatric and metabolic surgery

In the past decade, many scientific studies on long-term effects after sleeve gastrectomy (SG) have revolutionized diagnostics and treatment of vitamin deficiencies. Many new insights have emerged, and several international guidelines have included SG as a primary bariatric procedure since 2013 (4-6). It appears that vitamin deficiencies after SG have been underestimated for many years (7-9). This thesis has clearly shown that a large number of patients will develop vitamin deficiencies after SG, and therefore, lifelong use of a multivitamin supplement (MVS) is necessary.

In **Chapter 2** we observed the effectiveness of specialized weight loss surgery (WLS) MVS compared to a regular MVS. This study found that use of WLS MVS results in less vitamin B1, vitamin B12 and folic acid deficiencies. Overall, the number of patients having one or more deficiencies was significantly lower among WLS MVS users. On the contrary, more patients with anemia, iron deficiencies and hypervitaminosis B6 were diagnosed in the WLS MVS users group, which suggests that the iron dose is insufficient and vitamin B6 dosage too high. This retrospective study shows that SG patients could benefit even more from the specialized WLS MVS. However, high percentages of vitamin deficiencies are seen regardless of the use of either supplement. Key points in this discussion are the high percentage of vitamin deficiencies and occurrence of de novo deficiencies despite MVS use. This implies either a certain degree of malabsorption of supplements, interrupted patient adherence to MVS intake or a combination of both factors. It is difficult to control the patient's adherence to MVS intake. The use of MVS after bariatric surgery is not reimbursed in the Netherlands. Bariatric patients can purchase the supplements wherever they prefer, which makes registration of purchase impossible. In order to detect vitamin deficiencies, lifelong annual laboratory checks are necessary. Moreover, further insight into patient's adherence is important in the reduction of vitamin deficiencies.

Vitamin B12

Vitamin B12 deficiencies are common after bariatric surgery and may cause serious neurological complications. Although the first international guideline on nutritional surveillance in bariatric patients were published in 2008, there is still much unknown about the treatment of vitamin deficiencies (10). Two updated guidelines have been published in 2017 and 2019 (4, 5). However, inconclusive scientific evidence in the guidelines and conflicting results from other studies pose a challenge in the management of vitamin B12 deficiencies.

Chapters 3, 4 and 5 focused on detection and treatment of vitamin B12 deficiencies after bariatric surgery. Preventive vitamin B12 supplementation regimens and the treatment of vitamin B12 deficiencies were systematically reviewed in **Chapter 3**. Our systematic review suggests that a dose of at least 350 µg oral vitamin B12 daily can maintain normal levels of serum vitamin B12. Some obvious limitations need to be addressed such as the heterogeneity of the included studies, the small sample size (n = 10) and a lack of standardized outcome measurements. Therefore, definitive conclusions cannot be drawn. Currently, there is no consensus on the optimal treatment regimen for vitamin B12 deficiencies following bariatric surgery, which is confirmed by the results of our systematic review (10-13).

In **Chapter 4** we analyzed whether bariatric patients with serum vitamin B12 between 140 and 200 pmol/L would benefit from intramuscular (im) hydroxocobalamin injections. The definition deficiency was based on serum methyl malonic acid (MMA): 'deficient' was defined as serum MMA > 300 nmol/L and 'not deficient' was defined as serum MMA < 300 nmol/L. This study shows that all vitamin B12 deficient patients benefit clinically from this treatment and MMA normalized in all deficient patients. However, positive results were also found for patients with complaints but without biochemical deficiency, which suggests that serum vitamin B12 is a poor predictor for the functional vitamin B12 status. Patients with normal serum vitamin B12 values may have subclinical elevated MMA values and thus a subclinical deficiency. Therefore, diagnostics with two combined parameters is very important. This suggests that the lower reference limit of 140 pmol/L should be raised to 200 pmol/L and clinical symptoms must be considered as a subclinical vitamin B12 deficiency. Clinical symptoms should be a reason for vitamin B12 treatment on trial or further analysis with serum MMA. In case of vitamin B12 related symptoms and an elevated serum MMA concentration, but still within the normal reference range values, vitamin B12 treatment must be started.

One of the major strengths of this study is the use of the combined biomarkers serum vitamin B12 and serum MMA (14-16). We found more vitamin B12 deficiencies since these combined biomarkers have been measured, especially in patients with serum vitamin B12 below 200 pmol/L. Physiologically, this could be explained by the high failure rate of the biomarker serum vitamin B12, which makes detection and recognition of a deficiency difficult. Vitamin B12 is absorbed by active transport and passive transport (diffusion). Active transport occurs in the ileum when vitamin B12 is bound to intrinsic factor (IF), but the contribution of this transport is limited, since a significant part of the stomach is either removed or diverted after bariatric surgery. Bariatric patients are therefore largely dependent on passive absorption which occurs independent of IF along the entire length of the gastro-intestinal tract. Only 1% of orally administered vitamin B12 is absorbed by passive transport and therefore only important with the use of high dose vitamin B12 supplements. Once absorbed into the blood, vitamin B12 is bound to haptocorrin and transcobalamin (TC-I, TC-II and TC-III). However, haptocorrin is not primarily responsible for delivering B12 to body tissues, because there are no haptocorrin receptors located on most cells. Only 20% bound to TC-II reaches the absorption into body tissues (15, 17-19). Serum MMA is a more sensitive marker, but expensive since more complex instruments and highly qualified staff is required for this measurement (18). Therefore, it is important to analyze which patients benefit most from the use of the combined biomarkers. With the results of Chapter 4, our obesity center increased the serum vitamin B12 cut-off value for im hydroxocobalamin treatment from 140 pmol/L to 200 pmol/L and no additional MMA measurements were needed in these cases. Laboratory costs could be reduced with this new algorithm. However, some limitations needed to be addressed. Firstly, renal function was not included in the algorithm. Serum MMA is affected by kidney function and therefore, patients with renal malfunction may have been misdiagnosed (19, 20). Secondly, only laboratory costs were reduced by using this algorithm. The costs of the treatment itself and medical consultations were not included and therefore cost effectiveness cannot be properly assessed. Thirdly, the small sample size, short follow-up, and retrospective character of this study.

In **Chapter 5,** different im hydroxocobalamin supplementation regimens were compared in a retrospective matched cohort study. One group received 6 im injections, one group received 3 im injections and the control group received no im injections. The short im injection treatment was not sufficient to treat all vitamin B12 deficiencies whereas all deficiencies were restored biochemically with 6 im injections. However, it is unclear how long these biochemical effects will last and when the first rise in serum MMA will become visible again. Consequently, the use of different types of MVS with different amounts of vitamin B12 and unreliable patient adherence to MVS intake could influence the serum concentrations. The included patient groups were too small to perform a sub-analysis between those different supplements. Therefore, his topic needs to be further investigated.

According to the results of Chapter 3, 4 and 5, the treatment of vitamin B12 deficiencies can be further optimized. Currently a lot of research is being done to show the effect of correcting vitamin B12 deficiencies biochemically with different supplementation regimens.

However, no clear advice can be given, because the clinical relevance of correcting these deficiencies is unclear and scientific evidence in international guidelines could be further improved. The key point in this discussion is the recognition of vitamin B12 deficiencies. Based on the results of the studies in this thesis, a biochemical algorithm with combined parameters was developed in the Catharina Hospital Eindhoven to facilitate earlier detection of vitamin B12 deficiencies. When MMA is included in the diagnostic process, a deficiency could be treated earlier in order to prevent serious neurological complaints (15, 18, 21). Further research must focus on the influence of renal function on serum MMA. Other interesting topics for future research are the clinical relevance of correcting these deficiencies, long-term effects of im hydroxocobalamin injections, the potential influence of a placebo effect and the adherence to MVS intake.

Vitamin D

Vitamin D deficiencies are common after bariatric surgery. Vitamin D is necessary for optimal musculoskeletal and bone health (22-24). Several underlying mechanisms including reduced sun exposure, reduced intestinal absorption, sequestration of vitamin D in adipose tissue and reduced renal activation play a role in the development of a deficiency (23, 25-27). In **Chapter 6**, we studied the biochemical effects of two different cholecalciferol treatment regimen. The intervention group received 800 IU daily (= 20 mcg daily) and 50,000 IU monthly (converted to daily amounts: 2466 IU = 61.6 mcg). The control group received the standard regimen of 800 IU daily. Eight hundred international units daily are not sufficient, because 70% of these patients were still deficient during follow-up. The addition of 50,000 IU cholecalciferol monthly resulted in less vitamin D deficiencies and a faster increase of serum 25-hydroxyvitamin D. Nevertheless, serum 25-hydroxyvitamin D values were still insufficient in 20% of patients in the intervention group. The treatment regimen in the intervention group was not sufficient to achieve serum 25-hydroxyvitamin D above 75 nmol/L in all patients. This suggests that the treatment dosage must be further increased. Current international guidelines for bariatric surgery advise 3000 IU – 6000 IU daily or 50,000 IU 1-3 times weekly to reach adequate serum concentrations (5). The study by Giustina et al. described that amounts greater than 10,000 IU may be required in the case of malabsorption (28). This advice greatly exceeds the European Food Safety Authority (EFSA) acceptable upper limit of 100 mcg (= 4000 IU) vitamin D intake per day (29). The conflicting opinions from the international guidelines for bariatric surgery and EFSA are an interesting topic of discussion. It can be postulated that higher vitamin D doses than described by EFSA are justified in cases of a persistent vitamin D deficiency, because the EFSA advice is based on a situation without anatomical changes or malabsorption. However, the actual functional absorptive capacity of the intestines is unclear after bariatric surgery. In addition, a severe and persistent vitamin D deficiency can lead to irreversible damage in the long-term as well as toxic serum vitamin D levels. A recommended toxic serum 25-hydroxyvitamin D limit after bariatric surgery is lacking. Literature on other patient populations reported toxic serum 25-hydroxyvitamin D levels above 220 nmol/L, because these levels were always accompanied by hypercalcemia (30). But it is unclear whether this toxic serum limit of 220 nmol/L can also be used in the bariatric patient population. Furthermore, other underlying factors for persistent deficiencies need to be investigated first. Patient adherence of supplement intake or gastro-intestinal symptoms such as diarrhea or steatorrhea can adversely affect the absorption of fat-soluble vitamins. However, a definitive conclusion cannot be made, because the influence of patient adherence and gastro-intestinal complaints were not included in this study. It is unclear whether the extended treatment regimen consists of an insufficient dosage or whether patient adherence is poor or both. Therefore, it is important to evaluate the effect of vitamin D supplementation by blood sampling to prevent vitamin D deficiencies.

The same patient database was also used for **Chapter 7**, where we studied the effect of the vitamin D supplementation regimens and the effect of protein intake on physical fitness. A lower handgrip strength (HS) is often present in patients with a vitamin D deficiency reported by Gumeiro et al. (24). However, HS outcomes in our study were not influenced by serum 25-hydroxyvitamin D, which is contradictory to other studies reported in literature (22, 24). Preoperative muscle strength and postoperative weight loss are other factors that could influence these HS outcomes. Muscle loss is observed in several fat-free-mass loss (FFML) reports after bariatric surgery (31, 32). Other vitamin deficiencies and malnutrition can influence these physical activities as well. Muscle function reacts early to nutritional deprivation. HS therefore has also become a popular marker of nutritional status and is widely used in many nutritional intervention studies (31). In this study, protein intake seems to influence postoperative HS outcome measurements, but not the shuttle walk run test (SWRT). This suggests that though protein intake is clearly important for postoperative muscle strength, it may be less important in terms of physical endurance. However, it is difficult to assess one responsible factor for these changes due to the small sample size and retrospective character of this study.

In our obesity center, the individual recommended protein intake was calculated by the dietician according to the AACE/ASMBS guidelines as 1.0 gram per kilogram ideal body weight (based on a BMI of 22.5 kg/m^2) (6). The individual protein intake was calculated by using a 24-hour dietary recall and an adequate intake was observed in 75% of all patients. Yet one of the biggest challenges in 24-hour dietary recall is to acquire reliable and accurate estimates of protein intake (33). Therefore, misreporting of protein intake may have influenced the outcomes of our study.

Following the results of Chapter 6 and 7, the treatment of vitamin D deficiencies needs to be further optimized and therefore, more research is necessary. Furthermore, an upper limit of serum 25-hydroxyvitamin D for this specific patient population is lacking and should be considered. This implies that international guidelines must be critically reviewed. There were some obvious limitations such as the retrospective character, a small study population and lack of information on patient adherence of supplement and protein intake. Only biochemical processes were considered in these studies. A randomized controlled trial including DEXA scan analyzes is necessary to determine the clinical relevance, such as osteoporosis risk and fracture incidence in the long-term.

Part II: Adherence to multivitamin supplementation after bariatric and metabolic surgery

Bariatric patients are advised to adhere to many lifestyle changes and life-long use of MVS after surgery. Many patients stop taking MVS or become less consistent with MVS intake over time, despite proven effectiveness and recommendations of the international guidelines. This could play an important role in the development of vitamin deficiencies (34-36). This thesis underlines the challenging task of nutritional management in bariatric surgery patients.

In **Chapter 8**, we attempted to learn which potential barriers influence poor adherence to MVS intake after bariatric surgery. These topics are scarcely described in the current literature and a systematic review could therefore not be performed. Instead, we tried to gain knowledge from other patient populations using chronic medication or supplementation in order to find potential factors that can improve patient adherence in the obese population. More insight into these factors is necessary to improve patient adherence to MVS intake after bariatric surgery. This narrative review served as a preliminary study for the next chapter.

Chapter 9 provides results of a multicenter survey study on patient adherence to MVS intake after bariatric surgery. This is the first comprehensive multicenter study that investigates this subject anonymously with a large sample size. According to this survey, the attitude of many bariatric patients towards MVS use is predominantly negative. The key reasons for cessation or inadequate intake of MVS were gastro-intestinal side effects, an unpleasant taste or smell of the MVS, normalized laboratory results, forgetting to take the MVS and the high cost of supplements. In addition to this, many patients were dissatisfied regarding the information provided from healthcare professionals about MVS and the little attention paid to MVS use during medical consultations. According to this survey, healthcare professionals often do not ask for beliefs and patient's personal preferences, which suggests that the patient-doctor relationship is inadequate.

There are three different parties who can improve patient adherence to MVS intake after bariatric surgery: the healthcare professionals, the MVS producers and the insurance companies with the Dutch Healthcare Authorities. Emphasizing the importance of MVS use after bariatric surgery needs to be further expanded by discussing the different therapeutic options, benefits, side effects and costs. A shared decision-making (SDM) process of MVS use should be introduced. SDM has a positive effect on the patient-doctor relationship and the extent to which patients are extensively informed about different therapy options. This increases patient's awareness during the decision-making process (37-41). Furthermore, the MVS producers can increase therapy adherence by further optimizing their supplements. MVS formulas should be adapted to reduce the high percentage of gastro-intestinal side effects after MVS intake and reduce the unpleasant size, taste, and smell of the supplements. Patients individually switch to other regular MVS ('over-the-counter') when high dose WLS formulas are not well tolerated. Moreover, insurance companies could contribute to patient adherence of MVS intake by reimbursing supplements, since costs are described as a common

reason for stopping WLS MVS. Therefore, it is essential that the Dutch Healthcare Authority acknowledges the importance of specialized WLS MVS to prevent vitamin deficiencies.
Some obvious strengths of the study need to be highlighted. Participation in this study was anonymous and there is no risk or personal benefit for patients. This reduces the risk of socially desirable answers. Furthermore, this study was performed in four high-volume obesity centers and therefore, the external validity is high.
The results of Chapter 8 and 9 have provided more insight into influencing factors of poor adherence to MVS intake. Results of Chapter 9 are an essential step towards better education and patient-tailored decision making. Historically, clinical decisions were made under a parternalistic model, in which the clinician used his/her knowledge and experience to make choices on behalf of the patient. Nowadays, with the accompanying rise in patient autonomy and patients' preference for participation in their healthcare decisions, the nature of clinical decision making is shifting from parternalistic to participatory. There is growing evidence that partients benefit greatly from taking a more proactive approach in their healthcare decisions. For instance, patients who are better informed about their treatment options are more likely to adhere to their treatments. Ensuring that patients receive the treatment that is most appropriate and preferable to them can increase patient satisfaction and recuce overall healthcare costs by avoiding unnecessary / unwanted treatment or to prevent for undertreatment or overtreatment (37-43). Furthermore, composition of WLS MVS should be further improved. The results of these chapters can be used for further hypothesis-generating research. A future interesting research topic could be to investigate if the type of bariatric procedure and time after surgery influences adherence to MVS intake. Which groups are at higher risk?
The relationship between healthcare professionals and patient needs to be further investigated to clarify discrepancies between experiences from healthcare professionals and those from a patient's perspective.

CONCLUSION AND FUTURE PERSPECTIVES

The growing prevalence of (morbid) obesity predicts a further increase in bariatric surgery worldwide. Therefore, gaining a better understanding of the nutritional consequences of bariatric surgery is paramount. Vitamin deficiencies after bariatric surgery are a serious threat and therefore early recognition and providing optimal treatment is crucial in every patient. This thesis underlines the challenging task of nutritional surveillance by healthcare professionals involved in obesity treatment.
This thesis shows that implementation of an algorithm with combined biomarkers serum vitamin B12 and serum MMA contributes to improved and faster detection of vitamin B12 deficiencies. Further research of this algorithm should focus on quantifying the effect of individual kidney function and different stages of renal impairment on serum MMA. Also,

different intramuscular hydroxocobalamin injection doses were analyzed for treatment of vitamin B12 deficiencies and a treatment regimen with less than 6 injections leads to insufficient biochemical improvement. An important topic for further research is the long-term effect of these treatment regimens on serum MMA. It appears that a subclinical vitamin B12 deficiency is common, as patients with clinical symptoms and without biochemical abnormalities improve after intramuscular hydroxocobalamin treatment. Vitamin B12 related complaints and abnormalities in laboratory results vary widely after bariatric surgery. Many patients do not fit within the advice of the international guidelines, which results in a large 'grey area'. Therefore, more attention should be paid to subclinical deficiencies and patient-tailored healthcare in the future.
The search for the most optimal vitamin D treatment is ongoing. Vitamin D deficiencies are common after bariatric surgery despite high-dose supplementation regimens. In addition, the upper limit of EFSA for daily vitamin D intake is exceeded with supplementation advice of current guidelines for bariatric surgery. The upper limit of EFSA is not tailored to the bariatric surgery patient. Higher vitamin D doses than described by EFSA can be justified in case of a persistent vitamin D deficiency, because of the malabsorption after bariatric surgery. Furthermore, other underlying factors for persistent deficiencies, such as patient adherence to supplement intake and gastro-intestinal symptoms, need to be investigated first and an upper limit of serum 25-hydroxyvitamin D for this specific patient population should be considered. This implies that international guidelines must be critically reviewed.
The search for the ideal specialized weight loss surgery (WLS) MVS for sleeve gastrectomy patients is still ongoing. This thesis shows that WLS MVS should be further improved to address iron deficiencies, hypervitaminosis B6 and many gastro-intestinal complaints after MVS intake. WLS MVS need to be further optimized by MVS producers to improve tolerability and reduce complaints after ingestion. Ideally, costs must be reduced to make WLS MVS accessible for more bariatric patients. Besides that, reimbursement of proven effective WLS MVS should be considered by the Dutch Healthcare Authority.
One of the most challenging topics to address is patient adherence to MVS intake. In addition to costs and reimbursement of supplements, the relationship between patient and healthcare professional is an important topic. Healthcare professionals are often not aware of the patient's experience on vitamin intake. There is growing evidence that partients benefit greatly from taking a more proactive approach in their healthcare decisions. For instance, patients who are better informed about their treatment options are more likely to adhere to their treatments. However, implementing shared decision making (SDM) into routine clinical practice at the obesity center has several challenges. Most challenging barrier to overcome is behavioral change and training of the healthcare professionals to involve the patient as an equal partner in the SDM process. Logistic and practical barriers are another challenging topic as well to SDM implementation, such as adjustments to clinical workflows and developing additional patient information tools.

Further research should focus on a better understanding of the relationship between patient and healthcare professional, as this could play a pivotal role in patient adherence. The results described in this thesis pave the way for further research on optimization of patient adherence to MVS intake in order to prevent vitamin deficiencies after bariatric surgery. Meanwhile, the focus should be turned towards proper follow-up with early recognition and treatment of vitamin deficiencies.
In conclusion, the development and treatment of vitamin deficiencies are areas of clinical care where the scientific evidence could be further improved. More attention should be paid on subclinical vitamin deficiencies and personalized care in the future. Underlying factors, such as patient adherence to supplement intake, are of greater importance and a multifactorial approach is essential to improve this adherence. Therefore, more focus should be on better education and improvement of the relationship between patient and healthcare professional.

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CHAPTER 11

Summary

SUMMARY

Bariatric surgery patients have a higher risk of developing nutritional deficiencies due to the anatomical alterations of the gastro-intestinal tract. Vitamin deficiencies is one of the most frequent problems within majority of bariatric patients. Therefore, prevention, detection and treatment of vitamin deficiencies are key aspects of long-term nutritional surveillance. The general aim of this thesis was to optimize all aspects regarding vitamin deficiencies after bariatric and metabolic surgery, of which patient adherence is the most important one. To achieve this aim, six research questions were defined to assess several important issues encountered in daily clinical practice:

1. Can we reduce the percentage of vitamin deficiencies by using the specialized weight loss surgery (WLS) multivitamin supplement (MVS)?
2. How can we improve the detection of vitamin B12 deficiencies after bariatric surgery?
3. What is the biochemical effect of different vitamin B12 supplementation regimens in deficient patients?
4. Does vitamin B12 treatment in patient with serum vitamin B12 between 140 and 200 pmol/L result in biochemical and clinical improvement?
5. What is the effect of different cholecalciferol supplementation regimens on biochemical outcomes and physical fitness?
6. Which factors and facilitators affect patient adherence to MVS intake?

Part I: Nutritional assessment in bariatric and metabolic surgery

In **Chapter 2** we compared the effectiveness of specialized WLS MVS compared with a regular MVS after sleeve gastrectomy (SG) in 970 patients. The use of WLS MVS resulted in significantly higher mean serum vitamin B1, vitamin D, vitamin B12, folic acid, and ferritin. WLS MVS resulted in less vitamin B1, vitamin B12 and folic acid deficiencies. Anemia, iron deficiencies and hypervitaminosis B6 were diagnosed more often in WLS MVS users, suggesting that the iron dose in this supplement is insufficient and vitamin B6 dosage too high. The total number of de novo deficiencies was significantly reduced during 4 years for all WLS-users. This shows that SG patients benefit from these specialized supplements. However, adjustments of WLS formulas are required for vitamin B6 and iron. This study shows the importance of lifelong follow-up, because WLS MVS cannot prevent all vitamin deficiencies.

In **Chapter 3**, we reviewed the biochemical effect of preventive vitamin B12 supplementation and different vitamin B12 treatment regimens in deficient patients. Ten studies were included in this systematic review.

The dosage of preventive oral vitamin B12 supplementation in all included studies varied from 1 µg/day to 600 µg/day. Eight of the included studies described significant persistence of vitamin B12 deficiencies when taking oral vitamin B12 doses below 350 µg/day. Therefore, this review suggests, that the oral dosage of vitamin B12 should be at least 350 µg/day in order maintain normal serum vitamin B12 concentrations. The influence of patient adherence to MVS use was only reported in two studies and remains therefore unclear.

In **Chapter 4**, we analyzed whether intramuscular (im) hydroxocobalamin injections in patients with serum vitamin B12 between 140 and 200 pmol/L results in improvement of serum vitamin B12, percentage of deficiencies and clinical symptoms. A vitamin B12 deficiency was defined as serum methyl malonic acid (MMA) > 300 nmol/L. All vitamin B12 deficiencies were treated successfully, and serum MMA normalized in all patients of the treatment group. Reported complaints in the intervention group (29%), such as tingling fingers, reduced attention span and tiredness, resolved after treatment. The control group, which did not receive im injections, showed a significant increase in serum MMA. In addition to this, the deficiency rate increased from 13% to 53% within six months, fortunately without increase of symptoms. This study shows that all vitamin B12 deficient patients benefit biochemically and clinically from im hydroxocobalamin treatment. However, beneficial effects were also found in patients without biochemical abnormalities, but with vitamin B12 related complaints. Patients with normal serum vitamin B12 values may have subclinical elevated serum MMA values and thus benefit from treatment. Therefore, diagnosis with combined parameters (serum vitamin B12 and MMA) is important. This study suggests that im treatment itself results in clinical improvement in patients with serum vitamin B12 between 140 and 200 pmol/L. With the results of this study an algorithm was developed and implemented at the obesity center of the Catharina Hospital Eindhoven (Figure 1).

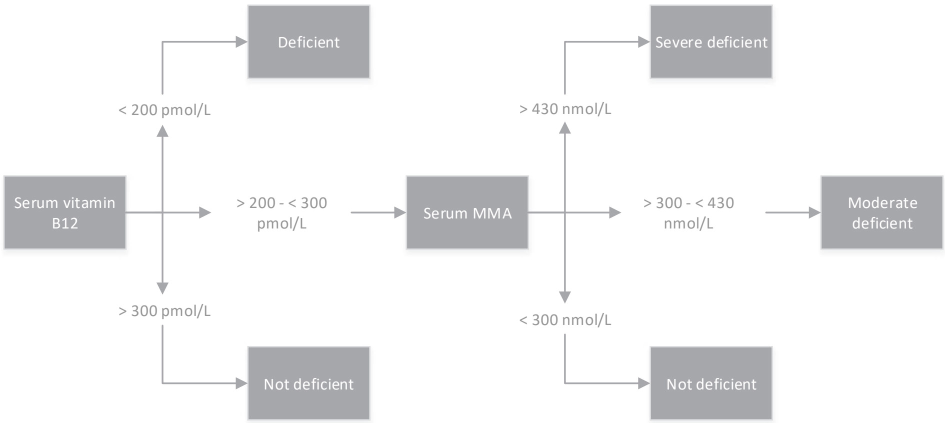

Figure 1: Algorithm for detecting vitamin B12 deficiency

In **Chapter 5**, we aimed to analyze the biochemical effects of different im hydroxocobalamin treatment regimen in a retrospective matched cohort study. Three regimens were compared in patients with a moderate to severe vitamin B12 deficiency based on serum MMA (Figure 1): three im injections, six im injections and a control group without im injections. Treatment with six im injections resulted in biochemical normalization, a faster decline of serum MMA and clinical recovery in all patients. Treatment with three im injections led to persistent deficiencies in 38% of the patients. All patients in the control group showed an increase of MMA without spontaneous improvements. In conclusion, this study suggests that a regimen with six im injections is sufficient to treat all vitamin B12 deficiencies biochemically.

In **Chapter 6**, we aimed to analyze the biochemical effects of two different cholecalciferol treatment regimens to prevent a vitamin D deficiency in a retrospective matched cohort study. Group A received 800 IU cholecalciferol daily and group B received 800 IU cholecalciferol daily and 50,000 IU cholecalciferol once per month. Serum 25-hydroxyvitamin D increased from 37.8 ± 20.6 nmol/L to 66.7 ± 18.5 nmol/L in group A versus 47.0 ± 21.5 nmol/L to 94.2 ± 25.7 nmol/L in group B. Persistent vitamin D deficiencies were observed in 70% and 20% after six months for group A and B, respectively. In conclusion, a cholecalciferol regimen with 800 IU daily and 50,000 IU monthly leads to a faster increase of serum 25-hydroxyvitamin D and less vitamin D deficiencies. However, this cholecalciferol regimen needs to be further optimized, as it is still not sufficient to treat all vitamin D deficiencies.

In our second vitamin D study (**Chapter 7**), the same database and cholecalciferol treatment regimens were used. We assessed the effect of the two cholecalciferol treatment regimens and protein intake on physical fitness in a retrospective matched cohort study. The protein intake was calculated by the dietician with a 24-hour food intake registration form three and six months after surgery. Outcomes of the handgrip strength (HS) and shuttle walk run test (SWRT) were used to analyze the effect on different supplementation regimens on physical fitness three and six months postoperatively. Outcomes of these two tests were assessed by the physiotherapist. Results showed that HS and SWRT were not significantly influenced by serum 25-hydroxyvitamin D. Multivariate analysis showed that protein intake influences postoperative HS outcome measurements only.

Part II: Adherence to multivitamin supplementation after bariatric and metabolic surgery

Chapter 8 attempted to clarify which potential barriers and facilitators influence patient adherence to MVS use after bariatric surgery. Because there is only limited data on this subject in bariatric patients, we gained knowledge from other patient populations with chronic medication or supplementation usage in order to find potential factors that can improve patient adherence in the obese population. Table 1 gives an overview of the negative influencing factors of this narrative review. These results were used to develop a questionnaire to assess patient adherence to MVS intake and served as a preliminary study for Chapter 9.

Table 1 Overview of this review of barriers who negatively influences patient adherence.

	Bariatric patients	Other patient populations
Patient-related factors	Age Gender Employment Postoperative complications Postoperative complaints Eating behavior	Age Low education levels and income
Therapy-related factors	Forgetting Swallowing Disintegration properties of MVS	Long duration of the medical treatment High frequency of daily dose Convenient way of administration Adverse effects of medication
Psychosocial and economic factors	High costs of MVS treatment	Patients lack belief in benefit of treatment Erroneous beliefs or misconception Negative attitude toward medication Treatment of asymptomatic disease Presence of psychological problems Forgetfulness or other priorities None or limited emotional support High costs of medical therapy
Healthcare-related factors	Cancelling yearly medical visits	Low satisfaction with clinical visits Inadequate follow-up due to missing appointments Discharge planning Poor patient-doctor relationship

MVS: multivitamin supplement

In **Chapter 9** we described the results of a cross-sectional multicenter survey study about patient adherence to MVS use after bariatric surgery. Four high-volume obesity centers in the Netherlands participated in the study and 15,424 patients were recruited. In total, 4614 patients (29.9%) were included in this study. Self-reported anonymized answers from MVS-users (n = 4274, 92.6%) were compared with those from the non-users (n = 340, 7.4%). Of all MVS users, 15.4% did not take MVS regularly. Most frequent reasons were 'forgetting daily intake' (68.3%), 'gastro-intestinal side effects' (25.6%) and 'unpleasant taste or smell' (22.7%). For non-users, the gastro-intestinal side effects after MVS intake (58.5%), costs (13.5%) and absence of deficiencies (20.9%) were the most frequent reasons to stop taking MVS. Most important differences between MVS uses and non-users were the occurrence of gastro-intestinal complaints (37.4% vs 26.3%) and the frequency of occurring. Non-users experienced post-prandial complaints multiple times a week or day whereas MVS users experienced these complaints less frequently. Half of all included patients indicated that these complaints were not discussed by the healthcare professional during medical consultation. Other significant differences between non-users and MVS users were costs of the supplements (61.2% vs. 39.4%) and many patients think that adherence to their MVS intake could improve by reimbursement of the supplements (43.5% vs. 38.1%).

Non-users were more often dissatisfied about instructions provided about MVS use. Attention paid to MVS use during medical consultations and the extent to which personal preferences of MVS use were also taken into account. Most frequent reasons for all included patients to score poor or inadequate (n = 1315, 28.5%) on the satisfaction scale was 'too general information' (57.1%), 'personal preferences are not taken into account' (51.0%) and 'not enough time for adequate information about MVS during medical consultation' (36.5%). Other reasons reported by patients were: 'too short consultation time' (23.5%), 'having to actively ask for information themselves' (28.9%), 'only being told what he/she is doing wrong' (9.4%) and 'only one MVS formula is advised by the healthcare professional' (6.5%).

In conclusion, the attitude of many bariatric patients towards MVS use is predominantly negative. This suggests it is important to provide more extensive information about different possibilities in MVS use. The advantages and disadvantages of MVS should be provided. In addition to this, beliefs and thoughts of the patient should be obtained in order to establish the patient's personal preferences. Challenges lie in improving patient adherence by implementing a shared decision-making process about MVS use, further optimization of the tolerance of WLS MVS formulas and exploring options for reimbursement of these specialized WLS MVS.

PART III

Appendices

DANKWOORD

Wat heb ik een unieke tijd gehad door als physician assistant (PA) een externe PhD te doen bij de Wageningen Universiteit! Ik wil alle patiënten bedanken voor deelname aan de onderzoeken. Ook wil ik iedereen bedanken die op welke wijze dan ook heeft bijgedragen aan de realisatie van mijn proefschrift, en een aantal mensen een speciaal woord van dank geven.

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Curriculum vitae

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Colophon

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