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Micronutrient status in morbidly obese patients undergoing bariatric surgery - assessment and intervention

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Although the benefits of bariatric surgery have been frequently proven, less is known about the micronutrient status of morbidly obese patients undergoing bariatric surgery. A deficiency in vitamin D pre- and postoperatively impairs bone, lipid, and glucose metabolism and increases the risk of osteomalacia and cardiometabolic diseases in these patients. However, there is a lack of reliable data on preoperative nutritional status and on the efficacy of adequate postoperative dietary measures with regard to vitamin D. Previous supplemental trials did not achieve the recommended serum 25-hydroxycholecalciferol (25-OHD) level of at least 50 nmol/L which is necessary to prevent a vitamin D deficiency. The aim of this thesis was to investigate whether obese patients are at risk of deficiency of several micronutrients which may postoperatively be related to nutrition-related diseases and may worsen malnourishment.

Within a cross-sectional study (CHAPTER ONE), the plasma/serum status of retinol, ascorbic acid, tocopherol, β-carotene, and 25-hydroxycholecalciferol were determined in 43 obese patients (body mass index: 52.6 ± 10.5 kg/m^2) before undergoing sleeve gastrectomy (SG), between April and June 2012. Moreover, markers to specify bone metabolism, like parathyroid hormone, alkaline phosphatase, calcium, phosphate, magnesium, and albumin were assessed. Dietary intake was estimated by 3 day food records. One-third of the patients had ascorbic acid levels below the cutoff value (< 28 nmol/L), additionally all patients had β-carotene levels ≤ 0.9 µmol/L. Retinol was below the cutoff value (< 0.7 µmol/L) in 5% of the patients, whereas the tocopherol/cholesterol-ratio was always above the cutoff value (> 2.8 µmol/mmol). 84% of the patients had 25-OHD levels below 50 nmol/L. The intake of pro-/vitamins were often below the corresponding reference values, but neither correlations between status and intake, nor associations between low serum/plasma levels and inadequate intakes were observed.

In a double-blind, placebo-controlled, randomized trial (CHAPTER TWO), 94 morbidly obese patients (body mass index: 51.8 ± 11.5 kg/m^2) underwent SG between June and October 2013. The verum group received an oily suspension (Vigantol oil®, diluted with Miglyol 812®) orally for 12 weeks after surgery providing 80 µg vitamin D_3 per day; the placebo group received an identical looking oil of middle chain triglycerides (Miglyol 812®) instead. Before the operation, then both 4 and 12 weeks after SG, 25-OHD, parathyroid hormone, alkaline phoshatase, calcium, magnesium, phosphate, glucose, triglycerides, total cholesterol, HDL and LDL cholesterol, creatinine, albumin, C-reactive protein, and TNF-α were analyzed in serum and HbA_{1c} was determined in EDTA-whole blood. Dietary intake of energy, macronutrients, and vitamin D were monitored using a 3 day food record. After 12 weeks, 25-OHD levels increased in 92% of the patients of the verum group to levels > 50 nmol/L and in 68% to levels > 75 nmol/L compared to only 54% and 22% of the patients in the placebo group, respectively. Vitamin D-related parameters of mineral metabolism and of cardiometabolic risk were not modulated by intervention. Adverse effects from the intake of the supplement containing vitamin D were not reported. The highest individual 25-OHD level observed after 12 weeks was 191 nmol/L, which was below the maximum safe level of 250 nmol/L.

In conclusion, many morbidly obese patients already suffer from subclinical deficiencies in multiple micronutrients, particularly concerning vitamin D, ascorbic acid, and β-carotene before undergoing SG. Measuring the preoperative micronutrient status will help when supplementing patients before surgery and in optimizing dietary strategies afterwards. High-dose vitamin D_3 supplementation by an oily preparation is an effective and safe measure to prevent vitamin D deficiency in obese patients after SG, but higher doses will be necessary to achieve 25-OHD levels > 75 nmol/L in all patients.

Obwohl die Wirksamkeit der Adipositaschirurgie erwiesen ist, ist wenig über den Mikronährstoffstatus morbid adipöser Patienten, die sich einem bariatrischen Eingriff unterziehen, bekannt. Ein prä- und postoperativ inadäquater Vitamin D-Status beeinträchtigt den Mineral-, Fett- und Glukosestoffwechsel und erhöht das Risiko für Osteomalazie und das kardiometabolische Risiko bei diesen Patienten. Verlässliche Daten zum präoperativen Mikronährstoffstatus und zur Wirksamkeit einer adäquaten postoperativen diätetischen Maßnahme zur Prävention eines Vitamin D Mangels liegen bisher nicht vor. In früheren Interventionsstudien konnte ein 25-Hydoxycholecalciferol (25-OHD)-Spiegel von mindestens 50 nmol/L im Serum, der zur Prävention eines Vitamin D Mangels notwendig ist, nicht erreicht werden. Das Ziel dieser Dissertation war es zu untersuchen, ob adipöse Patienten ein hohes Risiko für verschiedene Mikronährstoffmängel haben, die nach operativem Eingriff Mangelernährung verstärken und ernährungsbedingte Erkrankungen begünstigen können.

In einer Querschnittsstudie (Kapitel 1) wurden bei 43 adipösen Patienten (Body-Mass-Index: 52,6 ± 10,5 kg/m^2) vor Durchführung einer Schlauchmagen-Operation zwischen April und Juni 2012 die Konzentrationen der Vitamine A, C, E, sowie von β-Carotin und 25-Hydroxycholecalciferol im Serum/Plasma bestimmt. Weiterhin wurden verschiedene Parameter zur Beurteilung des Knochenstoffwechsels, wie Parathormon, alkalische Phosphatase, Kalzium, Phosphat, Magnesium, und Albumin im Serum analysiert. Der Lebensmittelverzehr wurde über 3-Tages-Ernährungsprotokolle erfasst. Die Konzentration von Vitamin C im Plasma war bei einem Drittel der Patienten unterhalb des Referenzwerts (< 28 nmol/L) und 100 % der Patienten hatten einen Mangel an β-Carotin (≤ 0,9 µmol/L). Vitamin A war bei 5% der Patienten unter dem Referenzwert (< 0,7 µmol/L), während das Vitamin E/Cholesterol-Ratio in allen Fällen über dem Referenzwert lag (> 2,8 µmol/mmol). 84% der Patienten hatten eine 25-OHD-Konzentration unter 50 nmol/L. Die Pro-/Vitaminzufuhr lag häufig unter den jeweiligen Referenzwerten, wobei weder Korrelationen zwischen Zufuhr und Serum-/Plasmaspiegeln, noch Assoziationen zwischen geringen Spiegeln in Serum/Plasma und unzureichender Zufuhr beobachtet werden konnten.

In einer doppelblinden, placebo-kontrollierten, randomisierten Studie (Kapitel 2) wurden 94 morbid adipöse Patienten (Body-Mass-Index: 51,8 ± 11,5 kg/m^2) eingeschlossen, bei denen zwischen Juni und Oktober 2013 eine Schlauchmagen-Operation durchgeführt wurde. Patienten in der Verumgruppe erhielten über einen Zeitraum von 12 Wochen nach der Operation oral ein öliges Supplement (Vigantol Öl®, verdünnt mit Miglyol 812®), das 80 µg Vitamin D_3 pro Tag enthielt. Patienten in der Plazebogruppe wurde stattdessen ein Öl mit mittelkettigen Triglyzeriden (Miglyol 812®) verabreicht. Präoperativ sowie 4 und 12 Wochen nach der Operation wurden die Serum Konzentrationen von 25-OHD, Parathormon, alkalischer Phosphatase, Kalzium, Magnesium, Phosphat, Glukose, Triglyzeriden, Gesamt-cholesterol, HDL- und LDL- Cholesterol, Kreatinin, Albumin, C-reaktivem Protein und TNF-α analysiert sowie das HbA_{1c} im Vollblut bestimmt. Die Zufuhr von Energie, Makronährstoffen und Vitamin D wurde über 3-Tages-Ernährungsprotokolle erfasst. Nach 12 Wochen stieg die 25-OHD Konzentration bei 92% der Teilnehmer der Verumgruppe auf > 50 nmol/L und bei 68% auf > 75 nmol/L an; in der Plazebogruppe wurden diese Werte nur von 54% bzw. 22% der Teilnehmer erreicht. Vitamin D-assoziierte Parameter des Mineralstoffwechsels sowie kardiometabolische Parameter wurden durch die Intervention nicht beeinflusst. Nach Einnahme des Vitamin D-haltigen Supplements wurden keine unerwünschten Effekte festgestellt. Die höchste individuelle 25-OHD Konzentration nach 12 Wochen war 191 nmol/L und lag unterhalb der sicheren Höchstkonzentration von 250 nmol/L.

Daraus lässt sich schlussfolgern, dass viele morbid-adipöse Patienten vor Schlauchmagen-Operation einen Mangel an verschiedenen Mikronährstoffen aufweisen, speziell an Vitamin D, Vitamin C und β-Carotin. Die präoperative Bestimmung des Mikronährstoffstatus kann daher hilfreich sein, um Patienten rechtzeitig vor Operation zu supplementieren und die Ernährungstherapie postoperativ anzupassen. Die Supplementierung einer hohen Dosis an Vitamin D über ein öliges Präparat ist eine wirksame und sichere Maßnahme, um einem Vitamin D Mangel bei adipösen Patienten bei Schlauchmagen-Operation vorzubeugen. Jedoch sind noch höhere Dosierungen notwendig, um 25-OHD-Spiegel von > 75 nmol/L bei allen Patienten zu erreichen.

AP	Alkaline phosphatase
BMI	Body mass index
CRP	C-reactive protein
CV	Coefficient of variation
d	Day
EDTA	Ethylene diamine tetraacetic acid
ELISA	Enzyme linked immunosorbent assay
f	Female
HbA_{1c}	Glycated hemoglobin
HDL	High density lipoprotein
HPLC	High performance liquid chromatography
IU	International units
LDL	Low density lipoprotein
m	Male
n	Sample size
n.a.	Not available
n.d.	Not determined
NS	Not significant
P	Level of significance
PTH	Parathyroid hormone
RE	Retinol equivalents
Rm ANOVA	Repeated measures ANOVA
SD	Standard deviation
SG	Laparoscopic sleeve gastrectomy
TE	Tocopherol equivalents
TC	Total cholesterol
TNF-α	Tumor necrosis factor-α
Toc/chol ratio	Tocopherol/cholesterol ratio
WHO	World Health Organisation
wk	Week
yr	Year
25-OHD	25-hydroxycholecalciferol

GENERAL INTRODUCTION

The prevalence of obesity has dramatically increased worldwide during the past several decades and has nearly doubled since 1980. Approximately over 200 million men and nearly 300 million women are obese, which represents more than 10% of the world's adult population [1, 2]. In Germany, the prevalence of obesity among adults stood at 20.1% in 2014 [3]. Morbid obesity is associated with various co-morbidities, including hypertension, insulin resistance, and other components of the metabolic syndrome and with a significant increase in morbidity and mortality [4]. Class III obesity, defined as having a body mass index (BMI) of $\geq$ 40.00 kg/m^2, has increased disproportionately throughout the past decade [1, 5] and is associated with a twofold higher risk of all-cause mortality, than class I obesity [6], defined as having a BMI of 30.00–34.99 kg/m^2 [1].

Bariatric surgery is widely performed with increasing frequency and is regarded as the most effective and durable therapy for severe obesity to obtain weight loss, to improve quality of life, and to reduce obesity-related co-morbidities [7, 8]. From 2003 to 2013, the number of bariatric procedures increased exceptionally quickly from around 146,000 to 469,000 worldwide [9, 10]. Laparoscopic sleeve gastrectomy (SG) is a bariatric surgery procedure, which has recently gained popularity. The percentage of SG from all bariatric procedures has increased markedly from 0.0% in 2003 to 37.0% in 2013 worldwide, with similar trends observed in Europe [9]. It is a single stage procedure, restricting the food capacity of the stomach and leading to changes in gut hormone profiles [11], and has been shown to achieve a mean excessive weight loss of 64.3% after 24 months [12]. The reduction in stomach size restricts distention and increases saturation, thus lowering the meal portion size [13].

Bariatric surgery procedures frequently cause diet-related diseases in the postoperative period [14]. Previous studies have shown that micronutrient deficiencies and malnutrition after bariatric procedures are a known risk if not treated appropriately [15]. Until quite recently, nutritional deficiencies were less expected after SG than after malabsorptive procedures as the small intestine is neither bypassed nor removed in SG. Nowadays, it has been shown that the distinction between restriction and malabsorption should possibly be neglected, a result of the much greater metabolic effects of bariatric surgery, as interaction with gut hormones (ghrelin, peptide YY, and incretins) are recognized [16].

Although the benefits of bariatric surgery have been proven on frequent basis, less is known about micronutrient status of patients undergoing bariatric surgery. Particularly, the prevalence of micronutrient deficiencies has hardly been investigated in patients undergoing SG and deserves further research [17]. Individuals with extreme obesity who qualify for bariatric surgery are frequently deficient in several micronutrients before surgery [18, 19], as obesity itself is a known risk factor for the appearance of micronutrient deficiency [20].

Compared to non-obese patients, many morbid-obese patients are at risk of micronutrient deficiencies in spite of their excessive food and energy intake [1].

The issues of micronutrient deficiencies in bariatric patients were recently reviewed [21]. Risk factors include 1) preoperative malnutrition with regard to the preference of high energy but low-dense food items [1]; 2) a decreased food intake postoperatively because of a reduced gastric volume [13], changes in the regulation of appetite, hunger, and satiation [11], changes in food tolerance or eating patterns [22]; 3) insufficient vitamin and mineral supplementation because of poor compliance with supplemental regimen or insufficient dosages of micronutrients in supplements [23]; and 4) postoperatively inadequate nutritional follow-up and laboratory monitoring. An insufficient preoperative nutritional status may jeopardize the success of surgery, and malnourishment may worsen postoperatively [24]. This situation might foster diet-related complications in the postoperative period, which could be avoided by an adequate clinical nutrition management of the bariatric surgery patient [25].

A 25-hydroxycholecalciferol (25-OHD) deficiency (i.e., 25-OHD levels < 50 nmol/L) is a well-known public health issue in Germany [26] and is highly prevalent in obese patients before [27, 28] and after [29, 30] bariatric surgery. Vitamin D is essential for the maintenance of calcium homeostasis and vitamin D deficiency may lead to abnormalities in bone metabolism promoting the development of osteomalacia and osteoporosis by lowering bone mineral density [31]. 25-OHD levels between 50 - 75 nmol/L contribute to the pathogenesis of low-grade inflammation and cardiovascular diseases [32], and vitamin D insufficiency (i.e., 25-OHD levels < 75 nmol/L) may increase cardiovascular risk [33]. As morbidly obese patients already suffer from various co-morbidities of the metabolic syndrome before surgery [7], an adequate vitamin D supply is of great concern for these patients. Most vitamin D is obtained by endogenous synthesis when exposed to UVB radiation, and only 20% of the vitamin D supply is derived from food [34]. In bariatric patients, vitamin D deficiency might be increased due to higher distribution volume (fat mass) for 25-OHD [35]. Therefore, endogenous synthesis may be insufficient in these patients to prevent vitamin D deficiency. The German, Austrian, and Swiss Societies for Nutrition recommend an intake of 20 µg/d vitamin D for healthy adults without endogenous vitamin D synthesis [34]. By comparison, the median vitamin D intake of the general population in Germany is 2.55 µg/d [36].

However, guidelines for the nutritional management of these patients recommend daily multivitamin supplementation after bariatric surgery [21]. Currently, it is not known whether this measure is sufficient to prevent micronutrient deficiencies in obese patients postoperatively or whether this supplementation is necessary at all. Over-the-counter multivitamin preparations provide only 5 µg vitamin D_3 per day; results of previous studies suggest this dosage to be too low to achieve 25-OHD levels of > 50 nmol/L or > 75 nmol/L [17]. Therefore, supplementation of a higher vitamin D dosage might be necessary. Vitamin D

status should be assessed preoperatively and treated in the case of a vitamin D deficiency. 25-OHD levels should be monitored after bariatric surgery in order to prevent consequences of vitamin D malnutrition.

Obesity is characterized by chronic inflammation accompanied by an increased sensitivity to oxidative stress because of depleted antioxidant pro-/vitamins [37]. A sufficient supply of antioxidant pro-/vitamins, like ascorbic acid and tocopherol, is required to lower markers of inflammation and to improve insulin sensitivity [38]. Extracellular status of retinol [39, 40], tocopherol [39, 40], ascorbic acid [40-42], and β-carotene (provitamin A) [43] were rarely analyzed in patients preoperatively. Fat-soluble vitamin deficiencies can lead to disorders of differing severity. Several factors contribute to an increased risk of vitamin A deficiency in patients undergoing bariatric surgery; these include oxidative stress, non-alcoholic steatohepatitis, and the intake of foods providing relatively low amounts of vitamin A. Retinol plays an important role for visual acuity, immunological activity, and for cellular proliferation and differentiation [44]. Previous case reports show severe ophthalmic complications and xerodermia in patients after bariatric surgery because of severe vitamin A deficiency [45]. Preoperatively, vitamin A deficiency has been recorded in up to 21% of obese patients [46]. Although the prevalence of vitamin E deficiency and its clinical implications are less known in the case of bariatric surgery, insufficient availability of this antioxidant vitamin may contribute to oxidative damage in bariatric patients [37].

Fruit and vegetables are the main sources of vitamin C and β-carotene and the consumption of fruit and vegetables is negatively associated with obesity [47]. In previous studies, vitamin C deficiency was found in up to 64% of obese patients undergoing bariatric surgery [40]. Like vitamin E, ascorbic acid has important antioxidant functions, but adverse effects of deficiencies on postoperative clinical outcomes have not been observed yet.

To date, nutritional intake has hardly been documented in patients undergoing bariatric surgery, and the relation between extracellular micronutrient status and nutrient intake has not been investigated so far. Dietary recommendations are important parts of the patients' care after bariatric surgery to ensure sustainable weight loss and an adequate micronutrient supply. Afterwards, patients suffer from micronutrient deficiencies despite routine supplementation of vitamins and minerals [48]. Current guidelines for the management of bariatric patients only provide rough approaches for the treatment of these patients before and after surgery. Therefore, perioperative nutritional assessment and compensation of micronutrient deficiencies postoperatively are needed to specify the nutritional therapy of these patients for routine clinical practice.

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PURPOSE OF THE THESIS

The objective of this thesis was to answer the following questions:

1) How many obese patients suffer from micronutrient deficiencies already before undergoing bariatric surgery?

2) Does the extracellular micronutrient level reflect the corresponding intake in these patients?

3) Does the administration of a high-dose vitamin D supplementation by an oily preparation prevent from postoperative vitamin D deficiency or vitamin D insufficiency in morbidly obese patients?

4) Does high-dose vitamin D supplementation improve parameters of mineral metabolism in these patients?

5) Does high-dose vitamin D supplementation influence parameters of cardiometabolic risk in these patients?

To answer these questions, two clinical studies were performed:

The cross-sectional study (CHAPTER ONE) aims to answer question 1) and 2) by investigating the status of several pro/-vitamins and minerals in morbidly obese patients before bariatric surgery and the association between extracellular nutrient levels and corresponding nutrient intake.

The randomized, placebo controlled and double-blinded clinical trial (CHAPTER TWO) was done to answer questions 3) to 5) by investigating the effect of a daily ingestion of an oral vitamin D supplement (80 µg in oil) for 12 weeks in morbidly obese patients after SG.

CHAPTER ONE

Preoperative micronutrient status in morbidly obese patients before undergoing bariatric surgery: results of a cross-sectional study

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Abstract

Background: Reliable information on micronutrient status before bariatric surgery is needed to optimize preoperative nutritional status and postoperative nutritional therapy.

Objective: To investigate the pro-/vitamin and mineral status and its association with nutrient intake in morbidly obese patients seeking bariatric surgery.

Setting: Klinikum Vest, Recklinghausen, Germany.

Methods: The cross-sectional study investigated retinol, ascorbic acid, tocopherol, and β-carotene (high-pressure liquid chromatography), 25-hydroxycholecalciferol (enzyme-linked immunosorbent assay), and calcium, phosphate, and magnesium (photometry) in serum/plasma in 43 patients (body mass index: 52.6 ± 10.5 kg/m^2) before sleeve gastrectomy. Albumin, parathyroid hormone, and alkaline phosphatase were analyzed. Data were compared with accepted cutoff values. Dietary intake was estimated by 3-day food records, and nutrient intake was compared with recommended values.

Results: One-third of participants had ascorbic acid concentrations <28 nmol/L. All patients had β-carotene levels ≤0.9 µmol/L, although retinol was below the cutoff value (<0.7 µmol/L) in only 5%. Tocopherol/cholesterol-ratio was always > 2.8 µmol/mmol. Of the patients, 84% had 25-hydroxycholecalciferol levels below 50 nmol/L. Parathyroid hormone was elevated in 23% (>6.5 pmol/L). Calcium, magnesium, and alkaline phosphatase were always, and phosphate was mostly (98%) above cutoff values. Intake of retinol (23%), ascorbic acid (55.8%), vitamin D (90.7%), tocopherol (48.8%), and β-carotene (<2.0 mg/d; 37.2%) were often below recommendations. Correlations between serum/plasma concentrations and nutritional intake and associations between low concentrations and inadequate intake were not observed.

Conclusions: Many morbidly obese patients in Germany suffer from deficiencies in multiple micronutrients, particularly vitamin D, ascorbic acid, and β-carotene before sleeve gastrectomy. Measurement of preoperative micronutrient status will help supplement patients before and optimize nutritional therapy after surgery.

Introduction

Obesity is a prevalent public health problem reaching epidemic proportions worldwide [1]. Specifically, the percentage of morbidly obese adults (body mass index [BMI] $\geq$40 kg/m^2) has increased disproportionally throughout the past decade [2]. Excessive obesity is associated with various co-morbidities, including hypertension, insulin resistance, and other disorders generally known as the metabolic syndrome. Often, conservative treatments to reduce weight are ineffective due to low compliance. Bariatric surgery in combination with lifestyle changes can be long-term effective to improve quality of life, to reduce co-morbidities, and to increase life expectancy [3].

Despite excessive energy intake, obese subjects are at risk of deficiency for essential micronutrients due to their preferred consumption of food that is high in energy, but low in nutrient density [1]. Insufficient nutritional status preoperatively, i.e., low plasma concentrations of antioxidants, may be a risk factor for surgical complications; moreover, malnourishment may worsen postoperatively due to food intolerance and reduced food intake [4]. Consequently, information on micronutrient status before surgery is needed to optimize pre- and postoperative nutritional therapy. Reliable plasma/serum analyzes of micronutrient status in morbidly obese patients are still limited; earlier studies mostly focused on vitamin D [5-11]. A 25-hydroxycholecalciferol (25-OHD) deficiency was frequently observed before [5-11] and after bariatric surgery [12]. Vitamin D deficiency (i.e., 25-OHD levels < 50 nmol/L) leads to abnormalities in calcium, phosphorus, and bone metabolism, which favors osteomalacia by lowering bone mineral density [13]. In addition, 25-OHD concentrations between 50 - 75 nmol/L are associated with disorders in lipid and carbohydrate metabolism [14] and may therefore increase cardiovascular risk [15]. Because obesity is often associated with chronic inflammation [16], insufficient availability of antioxidant pro-/vitamins may contribute to oxidative processes. When planning the study, few data for ascorbic acid [10, 17, 18], β-carotene [19], retinol [7, 17] and tocopherol status [7, 17] in serum or plasma were available. In morbid obesity, β-carotene [20] as well as tocopherol status [21] is known to be inversely associated with BMI, and chronic low levels of these micronutrients compromize their availability to tissues [19]. Therefore, morbid obesity may lead to increased micronutrient requirements and/or may impair luminal nutrient uptake. Unfortunately, none of the above-mentioned studies related extracellular micronutrient status to nutrient intake.

The primary aim of our study was to assess the status of micronutrients in morbidly obese patients seeking bariatric surgery. The secondary aim was to correlate extracellular nutrient levels with the corresponding nutrient intake.

Materials and Methods

Patients

Following a monocenter cross-sectional study, 43 consecutive participants (≥ 18 yr) scheduled for bariatric surgery were recruited at Klinikum Vest, Recklinghausen, Germany, from April to June 2012. Inclusion and exclusion criteria were defined according to the S3 guidelines "bariatric surgery" [3]. Ingestion of dietary supplements was defined as further exclusion criteria. The study protocol was approved by the Ethics Committee of Bonn University (no. 019/12) and by the Ethics Committee of the General Medical Council Westphalia-Lippe and the Medical Faculty of Munster. Written informed consent was obtained from all participants before enrollment.

Blood sampling

Venous blood was collected after an overnight fast between 8:00 and 10:00 a.m., 2 weeks before surgery. Blood was collected in tubes coated with ethylenediaminetetraacetic acid (EDTA) for the analysis of retinol, ascorbic acid, tocopherol, β-carotene, and parathyroid hormone (PTH) or no anticoagulant for the determination of 25-OHD, albumin, alkaline phosphatase (AP), calcium, magnesium, phosphate, creatinine, and cholesterol.

Preparation of blood samples

Within 1 h of blood sampling, samples were centrifuged (2000 × g, 4°C, 10 min) to obtain plasma and serum, respectively. For ascorbic acid analysis, EDTA plasma was stabilized with a solution of metaphosphoric and perchloric acid, as described previously [22], and the supernatant obtained after centrifugation was analyzed. In samples analyzed for retinol, tocopherol, and β-carotene, 10 µL of 0.05% (w/v in ethanol) butylhydroxytoluol was added to the EDTA plasma (500 µL) to protect against lipid peroxidation. Aliquots were stored at -30°C in Recklinghausen for future analyses of pro-/vitamins and PTH. After the study was completed, the samples were transported to Bonn on dry ice and stored at -80°C until analysis.

Anthropometric data

Body height and weight were determined under standard conditions (fasting state, light clothes without shoes) using a medical scale (Soehnle, Murrhardt, Germany) adapted for persons with a body weight up to 300 kg. The BMI was calculated as ratio of body weight and body height squared (kg/m^2) and evaluated according to the criteria of the World Health Organization for obesity [1].

Energy and nutritional intake

The dietary intake was determined by self-completed standardized 3-day food records. Quantities of foods consumed were estimated by using common household measures (e.g., slices, cups, pieces, teaspoons). To minimize inaccuracies, the participants were instructed in verbal and written form how to fill the records. A dietician reviewed all records with respect to plausibility and addressed the participants if data were not plausible. The daily intake of energy, macronutrients, fiber, and selected micronutrients was calculated using DGE-PC professional 4.0 (German Nutrition Society, Bonn, Germany) based on the German Nutrient Data Base (BLS, Bundeslebensmittelschlüssel) II.3.

Micronutrients in serum/plasma

Serum 25-OHD was measured using an enzyme-linked immunosorbent assay kit (coefficient of variation [CV]: 4.6%; IDS, Frankfurt/Main, Germany). High-pressure liquid chromatography with UV/Vis detection was used to determine the plasma concentration of ascorbic acid (CV: 1.8%) according to Steffan [23]. Retinol (CV: 2.7%), tocopherol (CV: 4.1%), and β-carotene (CV: 3.5%) were measured using high-pressure liquid chromatography separation and subsequent UV detection as described previously [22]. Concentrations were reported per liter plasma or serum except for tocopherol which was reported per mmol cholesterol. Pro/-vitamin analyses were performed in duplicate at the Department of Nutrition and Food Sciences, University of Bonn. Calcium (CV: 1.2%), magnesium (CV: 1.0%), and phosphate (CV: 1.4%) were analyzed photometrically in serum (Cobas 6000/c501, Roche, Mannheim, Germany) at Klinikum Vest. Serum calcium concentrations were corrected using the formula of Payne et al. [24] to avoid an underestimation of serum calcium in the presence of low albumin levels.

Clinical chemistry

Albumin (Tina-quant ALBT2, Roche) (CV: 4.0%), AP (CV: 1.8%), creatinine (CV: 1.2%), and cholesterol (Accutrend GC, Roche) (CV: 1.6%) were analyzed in fresh serum as part of routine clinical chemistry (Cobas 6000/c501, Roche) at Klinikum Vest. PTH was determined by IMMULITE® 2000 Intact PTH (Siemens Healthcare Diagnostics, Eschborn, Germany) at the Department of Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn (CV: 7.6%).

Statistics and evaluation

Statistical evaluation was performed using PASW 20.0 (SPSS Inc., Munich, Germany). Data are expressed as means and standard deviations in case of normal distribution or as medians and quartiles for data with skewed distribution. Correlations between the

concentrations of 25-OHD and PTH, 25-OHD and BMI, and the daily pro-/vitamins intake and their respective concentrations in serum or plasma were analyzed by Pearson's test. The association between serum/plasma concentration and intake of pro-/vitamins below the reference range was investigated by Fisher's exact test. Statistical significance was set at $P < 0.05$.

Cutoff values from the U.S. Endocrine Society were used to assess serum 25-OHD [25]. For PTH and corrected calcium, reference values were taken from Thomas [26] and from Suter [27] for all other laboratory parameters. We compared nutritive intake with corresponding reference values of the German, Austrian, and Swiss Nutrition Societies [28].

Results

Demographic and clinical data are presented in Table 1. Forty-three patients (27 women, 16 men) scheduled for bariatric surgery were included in this study.

Results on plasma/serum concentrations of micronutrients are summarized in Table 2. Of the patients, 86% had serum 25-OHD values < 50 nmol/L. As for ascorbic acid, one third of the patients were below the critical plasma concentration (28 µmol/L), but only 5% had plasma retinol levels below the cutoff value (<0.7 µmol/L). All participants showed physiologic plasma tocopherol concentrations, but 100% of the patients had inadequate β-carotene levels.

Despite most patients presenting albumin deficiency (88% had < 40 g/L), calcium levels corrected for albumin were all within the reference range. The concentrations of all other minerals analyzed were within the normal range in all patients (Table 2).

PTH concentrations were above the cutoff value (>6.5 pmol/L) in 23% of the participants. Serum AP (88 ± 22 U/L) and creatinine (74 ± 17 µmol/L) were normal in all patients. As expected, 25-OHD and PTH were inversely correlated ($P = 0.02$; $r = -0.4$) but not 25-OHD and BMI.

Data on energy and nutrient intake are summarized in Table 3. Vitamin D intake was below the recommendation of the German Nutrition Society of 20 µg/d [28] in 91% of patients. Intake of β-carotene was inadequate in more than two thirds of our patients, and half of them did not reach the reference values for the intake of retinol, ascorbic acid, and tocopherol. We did not find any correlations between serum/plasma concentrations and nutritional intake nor associations between low concentrations and inadequate intakes (Table 4).

Table 1: Demographic and clinical data

Parameter	Patients (n = 43)
Sex	
Male, n (%)	16 (37.2)
Female, n (%)	27 (62.8)
Age (years) [a]	44 ± 12
Weight (kg) [a]	154.1 ± 35.9
Body mass index (kg/m^2) [a]	52.6 ± 10.5
Obesity classes, I/II/III [b]	0/5/38
Co-morbidities, n (%)	
Hypertension	25 (58.1)
Diabetes mellitus	12 (27.9)
Arthrosis	15 (34.9)
Depression	15 (34.9)
Obstructive sleep apnea	12 (27.9)
Smoker, n (%)	10 (23.3)
Socio-economic status, n (%)	
Employed	16 (37.2)
Unemployed	16 (37.2)
Early retirement	8 (18.6)
No information	3 (7.0)

[a] Mean ± SD; [b] Obesity class I: body mass index 30.00–34.99 kg/m^2; obesity class II: body mass index 35.00–39.99 kg/m^2; and obesity class III: body mass index $\geq$40.00 kg/m^2 (World Health Organization, 2000).

Table 2: Serum/plasma concentrations of micronutrients

	Patients [a]	Reference range [b]
25-Hydroxycholecalciferol (nmol/L)	35 ± 17	50–175 [c]
Retinol (µmol/L)	1.2 ± 0.4	0.7–1.75
Ascorbic acid (µmol/L)	32 ± 15	28–85
Toc/chol ratio (µmol/mmol)	5.5 ± 1.0	>2.8
β-Carotene (µmol/L)	0.3 ± 0.1	0.9–4.6
Calcium [d] (mmol/L)	2.43 ± 0.10	2.25–2.5 [e]
Magnesium (mmol/L)	0.77 ± 0.06	0.65–1.05
Phosphate (mmol/L)	1.08 ± 0.18	0.77–1.45

Abbreviations: Toc/chol ratio = tocopherol/cholesterol ratio.

[a] Data are means ± SD based on data from 43 patients for all parameters except for β-carotene (n = 23).

[b] Suter (2008) if not indicated otherwise.

[c] U.S. Endocrine Society.

[d] Calcium corrected for albumin.

[e] Thomas (2012).

Table 3: Daily energy and nutrient intake

	Daily intake [a]	Reference value for adults [b]
Energy (kcal/d)	2179 (1340–3113)	Age-related [c]
Protein (g/d)	77 (56–140)	-
Protein (g/kg weight) [d]	1.3 (0.9–1.9)	0.8
Fat (g/d)	77 (44–123)	-
Fat (energy %)	36 (27–44)	≤30
Carbohydrates (g/d)	200 (128–276)	-
Carbohydrates (energy %)	42 (37–51)	>50
Fiber (g/d)	20.1 (15.2–26.3)	≥30
Vitamin D (µg/d)	2.5 (1.6–4.5)	20
Retinol (mg RE/d)	1.4 (0.8–2.2)	1.0 (m); 0.8 (f)
β-Carotene (mg/d)	2.7 (1.6–4.7)	2–4
Ascorbic acid (mg/d)	85.7 (49.5–188.3)	100/150 [e]
Tocopherol (mg TE/d)	11.1 (7.9–19.3)	age related (m) [f]; 12 (f)
Calcium (mg/d)	985 (647–1380)	1000
Magnesium (mg/d)	402 (247–502)	age related [g]
Phosphate (g/d)	1.38 (1.00–2.00)	0.7

Abbreviations: m = male, f = female, RE = retinol equivalents, TE = tocopherol equivalents.

[a] Data are medians (interquartile range) based on 40 subjects.

[b] Reference values for nutritional intake of the German, Austrian, and Swiss Nutrition Societies (DACH, 2013).

[c] Estimated energy requirements considering a physical activity level of 1.4: <25 yr, 2500 kcal/d (m) and 1900 kcal/d (f); 25 to <51 yr, 2400 kcal/d (m) and 1900 kcal/d (f); 51 to <65 yr, 2200 kcal/d (m) and 1800 kcal/d (f); and >65 yr, 2000 kcal/d (m) and 1600 kcal/d (f).

[d] Related to reference weight, i.e., weight at BMI of 22 kg/m^2 (f) and 24 kg/m^2 (m).

[e] Non-smoker/smoker.

[f] <25 yr: 15 mg/d, 25 to <51 yr: 14 mg/d, 51 to <65 yr: 13 mg/d, and >65 yr: 12 mg/d.

[g] <25 yr: 400 mg/d (m) and 310 mg/d (f), >25 yr: 350 mg/d (m) and 300 mg/d (f).

Table 4: Relations between micronutrient status in serum/plasma and dietary intake

	Correlation between serum/plasma status and dietary intake	Association between serum/plasma status and intake below reference range
25-OHD (nmol/L) versus vitamin D intake (µg/d)	- 0.104	0.074
Retinol (µmol/L) versus vitamin A intake (mg RE/d)	0.207	0.131
Ascorbic acid (µmol/L) versus vitamin C intake (mg/d)	- 0.094	0.087
Toc/chol ratio (µmol/mmol) versus vitamin E intake (mg TE/d)	- 0.108	n.a.
β-Carotene (µmol/L) versus β-carotene intake (mg/d)	- 0.072	n.a.

Abbreviations: 25-OHD = 25-hydroxycholecalciferol; n.a. not available; RE = retinol equivalents; TE = tocopherol equivalents; Toc/Chol = Tocopherol/cholesterol-ratio.

Data present correlations by Pearson (correlation coefficients) and associations by Fisher's Exact test (contingency coefficients). For β-carotene and vitamin E, associations between plasma status und dietary intake could not be determined because β-carotene concentration was always below and tocopherol/cholesterol ratio always above corresponding reference values. Correlations and associations were not significant for any pro-/vitamin.

Discussion

To the authors´ knowledge, this is the first study investigating both nutrient status and intake of a broad spectrum of "critical" micronutrients in morbidly obese patients before undergoing bariatric surgery. In many participants, both plasma/serum concentrations and intake of vitamin D, ascorbic acid, and β-carotene were below reference values.

To assess nutrient status, we compared our laboratory data with actual cutoff values published for healthy, normal-weight adults [26, 27]. Because whole body distribution volumes are considerably higher in morbidly obese individuals than in their normal weight counterparts (especially for fat-soluble pro/-vitamins [29]), a dilution effect may occur. Nevertheless, the finding that the participants were deprived of several pro-/vitamins such as vitamin D, ascorbic acid, and β-carotene (Table 2) (in line with the primary hypothesis) supports the idea that the supply by food and/or by endogenous synthesis was not sufficient to ensure physiological micronutrient/metabolite concentrations. Their plasma concentrations were about half as much as in adults of the general population in Germany [30].

One third of the present patients had ascorbic acid levels below the cutoff level (<28 µmol/L), reflecting the low intake observed in nearly 50% of participants (Table 3). Using different cutoff values, previous studies in morbidly obese patients found lower (8.6% <17 µmol/L [31] and 15% <17 µmol/L [32]) or higher prevalence (63% <11 µmol/L [17]; 47% <26.1 µmol/L [18]; and 36% <33.5 µmol/L [32]) of ascorbic acid deficiency; none of these studies, unfortunately, reported data on nutrient intake.

In all of the present patients, β-carotene levels in plasma were below the defined cutoff value (<0.9 µmol/L); this result contrasts with 2 earlier studies performed in Brazil. Pereira et al. showed only 47% of obese patients had β-carotene values below the cutoff (<1.05 µmol/L), and Donadelli et al. reported <2% of obese patients were deficient, although they used a slightly lower cutoff (<0.7 µmol/L) than in the present study [31, 33]. Obviously, the mean consumption of fruit and vegetables in our patients (men 2.4 portions/d, women 2.6 portions/d) was lower than the fruit and vegetable consumption in the German Health Interview and Examination Survey for Adults (men 2.4 portions/d, women 3.1 portions/d) [34] and did not achieve 5 portions per day recommended by the German Nutrition Society [28]. This may be at least partly explained by the generally low socio-economic status of patients in the present study (Table 1), which may be associated with low fruit and vegetable consumption [34, 35]. The Brazilian patients [31, 33] may have had different food preferences than our German study group, leading to a better β-carotene status. From the physiological point of view, it should be kept in mind that an increased sequestration of β-carotene in fat tissue may be responsible for the low β-carotene status in obese patients [36]. Low levels of carotinoids in obese patients may also result from oxidative stress induced by obesity-related

inflammation [19, 20]. Low albumin concentrations as observed in our study group support this hypothesis. It can be cautiously interpreted that obese subjects need a considerably higher micronutrient intake to maintain physiological blood levels.

Despite inadequate plasma β-carotene status, only 5% of the present patients had plasma retinol levels below cutoff value (<0.7 µmol/L). Similarly, previous studies showing retinol concentrations below cutoff values (0.7–1.2 µmol/L) were either rarely prevalent (<9%) [17, 31] or not found [7, 8, 11, 17]. In line with previous studies in obese subjects [7, 8, 11, 18] and healthy German adults [37], all of the present patients had an adequate tocopherol status (Table 2). Obviously, high fat stores ensure physiological levels of retinol and tocopherol.

Using a generally accepted cutoff value of 50 nmol/L for 25-OHD [25], 84% of the present participants were deficient in 25-OHD. An objective comparison to other studies is difficult because 25-OHD status in obese persons has shown a marked seasonal variation [38]. Ernst et al. [38] found a 3.8-fold higher prevalence for vitamin D deficiency in obese patients during the winter season (February–March) than in the summer season (August–September). Because the present study was conducted in spring, serum 25-OHD levels probably reflect mean values obtained throughout the year. Furthermore, earlier studies used different cutoff levels (25–80 nmol/L) to assess 25-OHD status.

However, a high prevalence of 25-OHD deficiency (up to 96%) has been shown in several studies of patients seeking weight loss surgery [5-9, 11, 17, 39-43]. Many morbidly obese patients reside indoors or cover their skin with clothes for psychological reasons. Thus, the low UVB exposure in these patients reduces endogenous 25-OHD synthesis. However, low serum concentration of 25-OHD in obesity may be attributed to decreased bioavailability of vitamin D from cutaneous and dietary sources due to increased sequestration of this lipid-soluble vitamin in adipose tissue [29]. Vitamin D deficiency is a general public health issue in Germany, its severity probably being influenced by weight. Median 25-OHD levels in participants of the German National Health Interview and Examination Survey 1998 (82% of men and 77% of women were non-obese) was higher (men 45.2 nmol/L, women 44.7 nmol/L) [44] compared to median 25-OHD level of 31.2 nmol/L in the obese participants.

Of the present patients, 23% had PTH levels above the cutoff value (>6.5 pmol/L) along with 25-OHD values <50 nmol/L. These findings reflect a secondary hyperparathyroidism (sHPT), because none of the patients had increased calcium or decreased phosphate concentrations in serum being characteristic of primary hyperparathyroidism. Presence of sHPT due to renal insufficiency was also excluded because serum creatinine was normal in nearly all patients and not accompanied by increased serum phosphate concentrations. Previous studies found sHPT in 8–49% of bariatric patients preoperatively [6-9, 40-43] according to PTH cutoff levels between 3.0–7.5 pmol/L [6-9, 17, 41-43]. However, the present patients did not show symptomatic vitamin D

deficiency, as indicated by low 25-OHD, elevated AP, and decreased serum calcium and phosphate. Therefore, the patients likely had a subclinical (biochemical) vitamin D deficiency. Hamoui et al. and Vage et al. observed increased AP activity in 4.3% [43] and 5.2% [5] of their patients, respectively, but they applied lower cutoff values (125 U/L [43] and 105 U/L [5]) than were applied in the present study (220 U/L).

The intake of pro-/vitamins did not correlate with the status in serum/plasma (Table 4). However, plasma retinol is homeostatically regulated and may derive partly from provitamin A carotinoids. Vitamin D status depends also on endogenous synthesis. Plasma tocopherol is regulated by the α-tocopherol transfer protein, by metabolism and excretion [45]. Concerning vitamin C and β-carotene, relationships between status and intake could be observed in the general population in Germany [37], but not in the present study. Reasons may be the low intake, an increased requirement owing to chronic inflammation, and an increased distribution volume in morbidly obese patients. Thus, low intake of vitamin A, C, D, E, and β-carotene in morbidly obese patients does not reflect an inadequate status. For these reasons, pro/vitamin analyses in serum/plasma are necessary.

The analytical methods used allow a reliable and sensitive determination of extracellular concentrations as a marker of nutrient availability. The characteristics of the patients were representative of morbidly obese individuals with regard to co-morbidities observed (Table 1). The diet of the present patients is likely to be typical for morbidly obese patients because participants were from different cities in the region of North-Rhine Westphalia, the central federal state in Germany.

Because of the novel approach of the present study, a sample size estimation could not be performed. However, the number of patients included may have been sufficient to draw conclusions. Although extracellular concentrations of pro-/vitamins do not necessarily reflect intracellular availability, they may provide initial evidence of a general insufficiency within the cell.

A strength of the present study was the investigation of several micronutrients in serum/plasma combined with nutrient intake. Moreover, the broad range of parameters related to vitamin D deficiency, including those of mineral metabolism, provided a clear estimation of the severity of vitamin D deficiency. However, the cross-sectional design of our study may be considered as limitation, because cause-and-effect relationships cannot be drawn.

Conclusions

Many morbidly obese patients in Germany suffer from multiple micronutrient deficiencies, especially vitamin D, ascorbic acid, and β-carotene, before bariatric surgery that may further worsen after surgery. Nutritional therapies should ensure a sufficient supply of ascorbic acid and β-carotene preoperatively by recommending increased consumption of fruit and vegetables. Routine analysis of these micronutrients in serum/plasma may be a reliable tool to objectively check nutritional behavior and to identify patients at risk for a biochemical deficiency. 25-OHD should be monitored and subclinical vitamin D deficiency should be compensated by vitamin D supplementation before bariatric surgery.

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CHAPTER TWO

High-dose vitamin D supplementation by an oily preparation prevents vitamin D deficiency in obese patients after sleeve gastrectomy - a double-blind, randomized, and placebo-controlled trial

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Abstract

Background: An inadequate vitamin D (VD) status impairs mineral, lipid, and glucose metabolism, thereby increasing the risk of osteomalacia and cardiometabolic diseases in morbidly obese patients. Former trials did not evaluate the efficacy of a fixed high-dose VD supplementation to prevent VD deficiency or insufficiency after bariatric surgery and its effect on biochemical parameters related to mineral metabolism and cardiometabolic risk in patients.

Methods: Morbidly obese patients (n = 94, BMI 51.8 ± 11.5 kg/m^2) received vitamin D_3 (80 µg/d in oil) or placebo in a randomized, double-blind, parallel-group study for 12 weeks after sleeve gastrectomy. 25-hydroxycholecalciferol (25-OHD), parameters on mineral, lipid, and glucose metabolism, C-reactive protein, and TNF-α were determined in serum/plasma before surgery and after 4 and 12 weeks of supplementation. Intake of energy, fat, and vitamin D were monitored using a 3-d food record.

Results: 79 Patients who finished the study according to protocol were included in statistical analysis. Preoperatively, 77.2% presented 25-OHD levels <75 nmol/L. After 12 weeks of supplementation, significantly more patients in the vitamin D group exhibit levels >50 nmol/L (92%) and >75 nmol/L (68%) compared to the placebo group (54% and 22%, respectively). Parameters of mineral metabolism and cardiometabolic risk were not modulated by intervention.

Conclusion: Supplementation of 80 µg/d VD_3 is an effective and safe measure to prevent VD deficiency in patients after sleeve gastrectomy, but higher doses will be necessary to achieve serum 25-OHD levels >75 nmol/L. Its effect on cardiometabolic risk remains unclear and should be investigated in future studies.

Introduction

Vitamin D (VD) deficiency, i.e., serum 25-hydroxycholecalciferol (25-OHD) levels < 50 nmol/L [1], has been commonly observed in morbidly obese patients prior to bariatric surgery [2-8]. This insufficient VD status often persists postoperatively, mostly in combination with elevated parathyroid hormone (PTH) levels [9]. In obesity, availability of VD from cutaneous and dietary sources is decreased due to its deposition in fat compartments [10]. Low VD intake by food, decreased UVB exposition, and low 25-hydroxylation in subcutaneous adipose tissue may be further reasons of VD deficiency in obesity [11].

VD deficiency decreases calcium and phosphorus absorption, thereby increasing PTH levels. PTH mobilizes calcium from the skeleton and increases renal reabsorption of calcium and excretion of phosphorus. Hence, VD deficiency disturbs calcium, phosphorus, and bone metabolism which favor osteomalacia by lowering bone mineral density [12]. As VD insufficiency, i.e., serum 25-OHD <75 nmol/L, was associated with disorders in lipid and glucose metabolism [13] and with metabolic syndrome [14], impaired VD status may increase the cardiometabolic risk in obese patients pre- and postoperatively.

In patients after undergoing laparoscopic sleeve gastrectomy (SG), supplementation of 20-50 µg/d VD_3 (800-880 IU) [9, 15-18] was insufficient to increase 25-OHD levels > 50 nmol/L, which may be explained by the reduced response with increasing body weight [19]. Supplementation of 50 µg/d VD_3 (2,000 IU) increased 25-OHD levels in obese patients 3 months after SG, but did not lead to 25-OHD levels > 50 nmol/L in all patients [16]. Probably, much higher doses are mandatory to perioperatively improve VD status in morbid obesity. Actual guidelines for perioperative support of the bariatric surgery patient recommend daily supplementation of VD titrated to 25-OHD levels of >75 nmol/L (3,000 IU) [20] which is suggested to maximize musculoskeletal health and to exert additionally cardiometabolic benefits [21].

However, evidence-based guidelines for optimal VD dosing strategies in patients after bariatric surgery are not available [22]. Providing a fixed dose is more feasible in routine clinical practice to prevent VD deficiency.

The aim of the present study was to assess the impact of high-dose VD_3 supplementation on VD status and on parameters of mineral metabolism and cardiometabolic risk in morbidly obese patients after SG.

Materials and Methods

Patients (≥18 yr) scheduled for bariatric surgery at Klinikum Vest, Recklinghausen, Germany, were consecutively included in this study, if they fulfilled the criteria of the S3 guidelines "bariatric surgery" [23] and did not ingest dietary supplements.

This randomized, double-blind, placebo-controlled, parallel-group trial was conducted at Klinikum Vest. Participants were allocated to VD or placebo group by permuted-block randomization using a block size of four (two patients per group). Patients and investigators were blinded to treatment until the end of the study.

The VD group supplemented 80 µg/d VD_3 for 12 weeks by a dilution of Vigantol oil® with Miglyol 812® (both from Merck, Darmstadt, Germany), an identical-appearing oil of medium chain triglycerides which served as placebo. Both were provided in single-dose ophtiols. The patients should ingest the preparations (1 mL) together with fatty foods and document the intake in a pre-build diary. The compliance was calculated as the percentage of ingested related to the total number of preparations. A compliance ≥ 80% was considered to be adequate.

Height was determined at wk_0 and weight at wk_0, wk_4, and wk_{12} under standard conditions. The BMI was evaluated by the WHO criteria for obesity [24].

Fasting blood was collected 2 weeks before (wk_0) and 4 weeks (wk_4) and 12 weeks (wk_{12}) after SG in tubes with EDTA and without anticoagulant. Serum 25-OHD was measured using an ELISA kit (IDS, Frankfurt/Main, Germany) and evaluated by using the cut-off values of the US Endocrine Society [1]. Intact PTH, albumin, alkaline phosphatase (AP), phosphate, magnesium, calcium, creatinine, glucose, total cholesterol (TC), HDL, LDL, triglycerides, and C-reactive protein (CRP) were analyzed in serum and glycated hemoglobin (HbA_{1c}) in whole blood by routine clinical chemistry. Calcium levels were corrected to avoid an underestimation in case of low albumin levels [25]. TNF-α was analyzed by TNF-α Quantikine HS ELISA kit (R&D Systems, Wiesbaden-Nordenstadt, Germany). Cut-off values for PTH, TNF-α, and corrected calcium (Ca_{corr}) were taken from Thomas [26] and from Suter [27] for further parameters.

The dietary intake was determined by standardized 3-d food records before and 3 weeks (wk_3) and 11 weeks (wk_{11}) after SG which were reviewed by a dietician with respect to plausibility. The intake of energy, fat, and VD was calculated using DGE-PC professional 4.0 (German Nutrition Society, Bonn, Germany) and compared with the reference values for healthy adults [28].

Patients were asked for adverse effects such as indisposition, eczema, nausea, and vomiting, which may occur by Vigantol oil®.

In a previous study of our group, mean 25-OHD level was 35 nmol/L [29]. A mean increase of 40 nmol/L was intended to achieve 75 nmol/L. In overweight/obese patients, supplementation of 83 µg/d VD_3 increased 25-OHD by 0.52 nmol/µg [30]. Therefore, 80 µg/d VD_3 seemed to be necessary to increase 25-OHD by 40 nmol/L. To detect an increase of ≥ 20 nmol/L by supplementation of 80 µg/d VD, 37 patients per group were needed presuming a power of 95%, $\alpha = 0.05$, $\beta = 0.10$, and a SD of 36 nmol/L. The minimum increase of 20 nmol/L reflects the difference between the intended increase and the change of 20 nmol/L which was considered to be significant [31]. The SD of the increase was calculated by considering the SD before [29] and after VD supplementation, and the correlation coefficient between both values. SD after VD supplementation and the correlation coefficient were estimated to be 36 nmol/L and 0.25, respectively, based on data of Zittermann et al. [30]. Assuming a dropout rate of 20%, 47 patients were included in each group.

Statistical evaluation was performed using IBM® SPSS 21.0. Between-group comparisons were done by χ^2 and Fisher's exact test for nominal variables, and by *t*-test for unpaired samples for metric variables if normal distribution could be assumed. Otherwise, Mann-Whitney-U-test was performed. The influence of time and intervention on metric variables was analyzed by repeated measures ANOVA and in case of significant effects by time, differences between time groups were investigated by Tukey test. If normal distribution failed, changes over time were analyzed by Friedman test. Statistical significance was assumed for $P \leq 0.05$. Metric data are presented as means and SEM or as median and quartiles if not indicated otherwise.

Results

94 patients were included between June and October 2013. Demographic, anthropometric, and clinical data were comparable between VD and placebo group (Table 1). As shown in Figure 1, 79 patients who finished the study according to the protocol were included in statistical analysis. These patients had initially higher 25-OHD levels (59.1 ± 23.7 nmol/L) than the dropouts (n = 11; 43.1 ± 11.3 nmol/L). They ingested on average 81 out of 84 preparations, indicating a mean compliance of 96%.

At baseline, laboratory data on VD and mineral metabolism did not differ between the groups (Table 2). VD supplementation affected 25-OHD level (P = 0.001) which changed over time in VD ($P \leq 0.001$) and placebo group (P = 0.003), but differences between two time point groups were only significant in the VD group. This group showed higher 25-OHD levels (Table 2) and larger increases in 25-OHD (Figure 2) after 4 and 12 weeks of intervention vs. baseline than the placebo group ($P \leq 0.001$ for all comparisons). Most patients (wk_4 97.4%; wk_{12} 92.1%) of the VD group achieved 25-OHD levels above 50 nmol/L, whereas the prevalence of VD deficiency did not change in the placebo group (Table 3). In the VD group, 68.4% of the patients achieved 25-OHD levels ≥ 75 nmol/L, but only 22% of the placebo group ($P \leq 0.001$).

Parameters of mineral metabolism were not affected by intervention. Effects by time were observed for PTH, albumin, Ca_{corr}, AP, creatinine, and phosphate ($P \leq 0.006$ for all comparisons), but significant differences between time point groups occurred only for albumin and Ca_{corr}. Despite the increase in Ca_{corr} after 12 weeks in the VD group (Table 2), all patients except one still had Ca_{corr} levels within the reference range (Table 3).

With regard to parameters of cardiometabolic risk, time-dependent effects occurred for triglycerides, TC, HDL, LDL, and for CRP ($P \leq 0.001$), but effects by treatment and interactions between treatment and time were not found for any parameter investigated (Table 4).

Energy and fat intake was only modulated by time. Energy intake decreased from 1971 ± 870 kcal/d (wk_0) to 364 ± 146 kcal/d ($P \leq 0.001$) (wk_3) and increased after 11 weeks to 646 ± 254 kcal/d (P = 0.003). 3 weeks after SG, less fat (12 ± 7 g/d) was ingested than preoperatively (79 ± 46 g/d, $P \leq 0.001$), followed by an increase after 11 weeks (26 ± 11 g/d, $P \leq 0.05$). Before SG, median VD intake from food was 1.8 [1.0; 3.7] µg/d. 2/3 of all patients followed the general advice to use a multivitamin preparation daily after a restrictive procedure [32] which increased total VD intake to 5.6 [5.3; 6.3] µg/d (wk_3) and 5.7 [5.3; 6.6] µg/d (wk_{11}) ($P \leq 0.001$). Patients who did not meet this recommendation ingested 0.5 [0.2; 0.8] µg (wk_3) and 1.1 [0.4; 1.8] µg (wk_{11}) VD daily after SG.

Adverse effects by the VD containing supplement were not reported.

Table 1: Demographic, anthropometric, and clinical data at baseline of the participants

Parameter	Vitamin D group (*n* = 47)	Placebo group (*n* = 47)
Sex		
Male, *n* (%)	16 (34.0)	18 (38.3)
Female, *n* (%)	31 (66.0)	29 (61.7)
Age (y)	43 ± 11	43 ± 10
Body weight (kg)	149.2 ± 32.3	156.2 ± 25.5
BMI (kg/m^2)	46.7 (44.6; 57.4)	50.0 (46.3; 58.8)
Obesity classes, I/II/III [a]	1/3/43	0/0/47
Comorbidities, *n* (%)		
Hypertension	29 (61.7)	31 (66.0)
Diabetes mellitus	12 (25.5)	14 (29.8)
Arthrosis	3 (6.4)	3 (6.4)
Depression	7 (14.9)	4 (8.5)
Obstructive sleep apnea	15 (31.9)	19 (40.4)
Degenerative alterations	27 (57.4)	28 (59.6)
Socio-economic status, *n* (%)		
Employed	9 (19.1)	11 (23.4)
Unemployed	7 (14.9)	4 (8.5)
Early retirement	28 (59.6)	30 (63.8)
No information	3 (6.4)	2 (4.3)

Metric data are means±SD and medians with quartiles in parentheses; respectively.

Data refer to all patients who were included in the study. No significant differences between the groups according to χ^2-test (nominal/ordinal data), unpaired *t*-test (metric data, except for BMI), and Mann-Whitney-U test (BMI).

[a]Obesity class I: BMI 30.00–34.99 kg/m^2, obesity class II: BMI 35.00–39.99 kg/m^2, and obesity class III: BMI $\geq$40.00 kg/m^2 according to WHO [(24)].

Table 2: Biochemical parameters of mineral metabolism before and 4 and 12 weeks after intervention

	Vitamin D group (n = 38)			Placebo group (n = 41)			Rm ANOVA		
	Wk_0	Wk_4	Wk_{12}	Wk_0	Wk_4	Wk_{12}	Treatment	Time	Treatment x time
25-Hydroxycholecalciferol (nmol/L)	60 ± 3 [a]	86 ± 4 [b]	92 ± 6 [bc]	58 ± 4 [a]	67 ± 5 [a]	58 ± 4 [a]	***	***	***
Parathyroid hormone (pmol/L)	4.1 ± 0.3 [a]	4.5 ± 0.4 [a]	4.7 ± 0.5 [a]	4.7 ± 0.4 [a]	5.5 ± 0.4 [a]	5.4 ± 0.4 [a]	NS	**	NS
Albumin (g/L)	37 ± 1 [ab]	38 ± 0 [a]	36 ± 1 [b]	37 ± 1 [a]	37 ± 1 [a]	36 ± 1 [a]	NS	***	NS
Calcium (mmol/L)	2.44 ± 0.01 [ab]	2.40 ± 0.01 [a]	2.47 ± 0.02 [b]	2.42 ± 0.01 [a]	2.43 ± 0.02 [a]	2.47 ± 0.02 [a]	NS	**	NS
Magnesium (mmol/L)	0.81 ± 0.01	0.79 ± 0.01	0.81 ± 0.01	0.80 ± 0.01	0.80 ± 0.01	0.81 ± 0.02	NS	NS	NS
Alkaline phosphatase (U/L)	77 ± 3 [a]	70 ± 3 [a]	69 ± 3 [a]	82 ± 3 [a]	72 ± 3 [a]	74 ± 3 [a]	NS	***	NS
Creatinine (µmol/L)	74 ± 3 [a]	79 ± 4 [a]	76 ± 3 [a]	73 ± 3 [a]	79 ± 4 [a]	71 ± 2 [a]	NS	***	NS
Phosphate (mmol/L)	1.05 ± 0.03 [a]	1.01 ± 0.02 [a]	1.06 ± 0.02 [a]	1.09 ± 0.03 [a]	1.02 ± 0.03 [a]	1.07 ± 0.03 [a]	NS	**	NS

Data are means±SEM. Patients who adequately adhered to the protocol and who ingested at least 80% of target dose were included in this analysis. Data were comparable between the groups at baseline according to the t-test for unpaired samples. Calcium was corrected for albumin.

**$P \leq 0.01$, ***$P \leq 0.001$ according to repeated measures ANOVA. In case of significant effects by time, Tukey test was performed. Means within a group without a common superscript letter differ significantly ($P \leq 0.05$).

Table 3: Biochemical parameters of mineral metabolism before and 4 and 12 weeks after intervention - patients below or above cutoff value, *n* (%)

	Vitamin D group (*n* = 38)			Placebo group (*n* = 41)			Cutoff value
	Wk_0	Wk_4	Wk_{12}	Wk_0	Wk_4	Wk_{12}	
25-Hydroxycholecalciferol	15 (39.5)	1 (2.6)	3 (7.9)	17 (41.5)	14 (34.1)	19 (46.3)	< 50 nmol/L[a]
	9 (23.7)	27 (71.1)	26 (68.4)	9 (22.0)	18 (43.9)	9 (22.0)	> 75 nmol/L[a]
Parathyroid hormone	4 (10.5)	4 (10.5)	5 (13.2)	8 (19.5)	12 (29.3)	7 (17.1)	> 6.5 pmol/L[b]
Albumin	33 (86.8)	33 (86.8)	32 (84.2)	30 (73.2)	33 (80.5)	31 (75.6)	< 40 g/L[c]
Calcium[d]	0 (0)	1 (2.6)	1 (2.6)	0 (0)	2 (4.9)	2 (4.9)	< 2.25 mmol/L[b]
Magnesium	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.9)	< 0.65 mmol/L[c]
Alkaline phosphatase	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	> 220 U/L[c]
Creatinine	2 (5.3)	2 (5.3)	1 (2.6)	1 (2.4)	3 (7.3)	1 (2.4)	> 110 µmol/L[c]
Phosphate	2 (5.3)	1 (2.6)	1 (2.6)	2 (4.9)	1 (2.4)	1 (2.4)	< 0.77 mmol/L[c]

Patients who adequately adhered to the protocol and who ingested at least 80% of target dose were included in this analysis.

[a]US Endocrine Society [(1)]; 25-hydroxycholecalciferol levels <50 nmol/L are defined as VD deficiency and levels > 75 nmol/L as sufficiency

[b]Thomas [(26)]

[c]Suter [(27)]

[d]Calcium corrected for albumin

Table 4: Parameters on cardiometabolic risk factors before and 4 and 12 weeks after intervention

	Vitamin D group (n = 38)			Placebo group (n = 41)			Rm ANOVA		
	Wk_0	Wk_4	Wk_{12}	Wk_0	Wk_4	Wk_{12}	Treatment	Time	Treatment x time
Glucose (mmol/L)	5.4 (5.0; 5.9) [a]	5.1 (4.9; 5.8) [a]	5.0 (4.7; 5.7) [a]	5.4 (5.0; 6.4) [a]	5.2 (4.8; 6.1) [ab]	4.8 (4.6; 5.5) [b]	–	–	–
HbA_{1c} (%)	5.5 (5.3; 6.1) [a]	5.4 (5.1; 5.8) [a]	5.2 (5.0; 5.6) [a]	5.6 (5.4; 6.4) [a]	5.6 (5.3; 6.1) [ab]	5.3 (5.1; 5.5) [b]	–	–	–
Triglycerides (mmol/L)	1.56 (1.30; 2.00) [a]	1.50 (1.28; 1.88) [ab]	1.23 (1.09; 1.65) [b]	1.90 (1.34; 2.52) [a]	1.59 (1.30; 2.09) [ab]	1.37 (1.14; 1.69) [b]	NS	***	NS
Total cholesterol (mmol/L)	4.68 (4.43; 5.88) [a]	4.24 (3.77; 4.89) [b]	4.72 (4.05; 5.49) [ab]	4.95 (4.45; 5.65) [a]	4.19 (3.75; 4.91) [b]	4.60 (4.14; 5.30) [ab]	NS	***	NS
HDL (mmol/L)	1.11 (0.95; 1.32) [a]	1.02 (0.93; 1.16) [b]	1.25 (1.04; 1.38) [ac]	1.12 (0.91; 1.34) [a]	0.95 (0.86; 1.19) [a]	1.09 (0.95; 1.35) [a]	NS	***	NS
LDL (mmol/L)	3.09 (2.78; 3.83) [a]	2.53 (2.27; 3.49) [b]	3.14 (2.47; 3.81) [ab]	3.34 (2.73; 3.89) [a]	2.67 (2.25; 3.39) [b]	3.03 (2.51; 3.62) [ab]	NS	***	NS
TNF-α (pg/mL)	2.3 (2.0; 3.2)	n.d.	2.5 (2.2; 3.4)	2.8 (2.2; 3.3)	n.d.	2.8 (2.3; 3.8)	NS	NS	NS
C-reactive protein (mg/L)	5 (3; 12) [a]	4 (1; 7) [a]	2 (1; 6) [a]	7 (6; 11) [a]	4 (2; 7) [b]	5 (3; 9) [ab]	NS	***	NS

Data are medians and quartiles in parentheses. Patients who adequately adhered to the protocol and who ingested at least 80% of target dose were included in this analysis. Groups were comparable at baseline according to unpaired t-test (lipids, TNF-α, C-reactive protein) and Mann-Whitney-U-test ($HbA_{1c,}$ glucose).

For HbA_{1c} and glucose, changes over time were investigated by Friedman-test. ***$P < 0.001$ according to repeated measures ANOVA. In case of significant effects by time, Tukey test was performed. Means within a group without a common superscript letter differ significantly ($P \leq 0.05$). n.d.: not determined

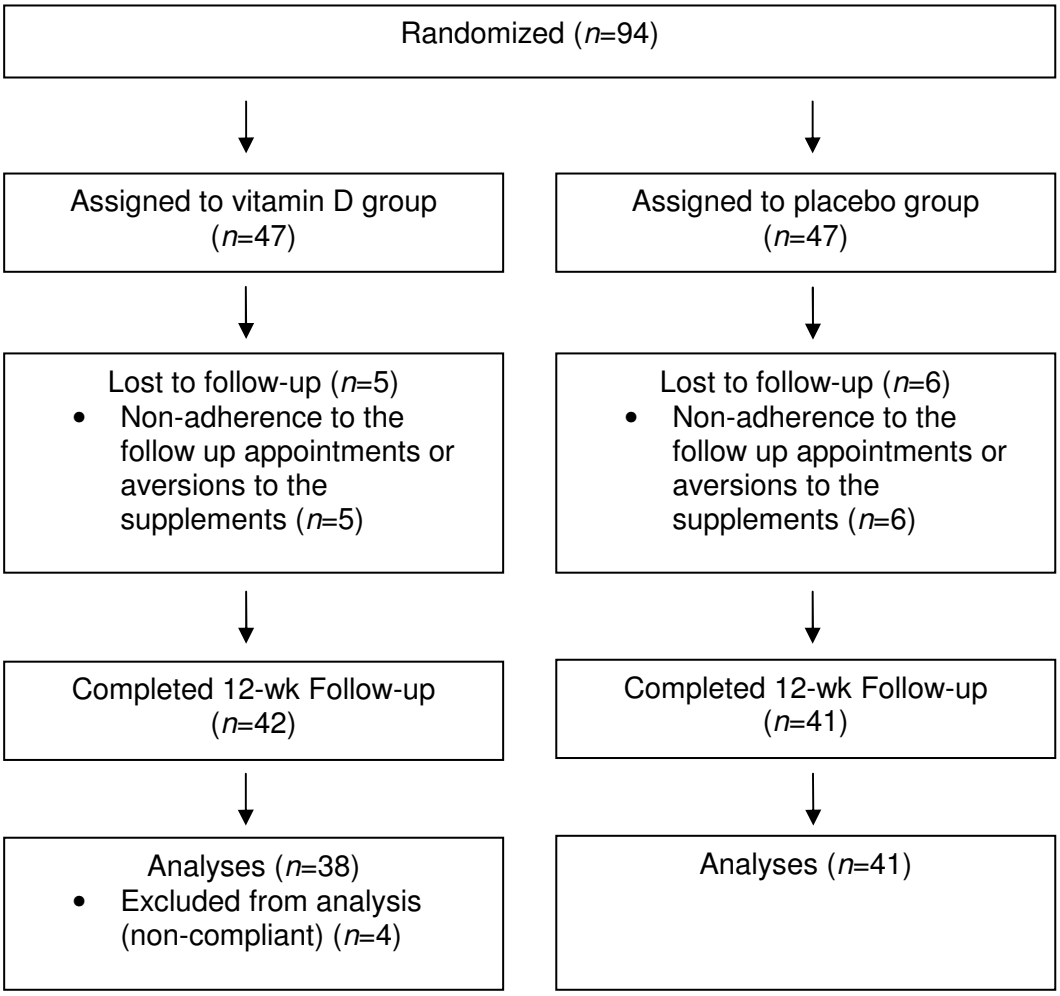

Figure 1: Flow of participants throughout the trial

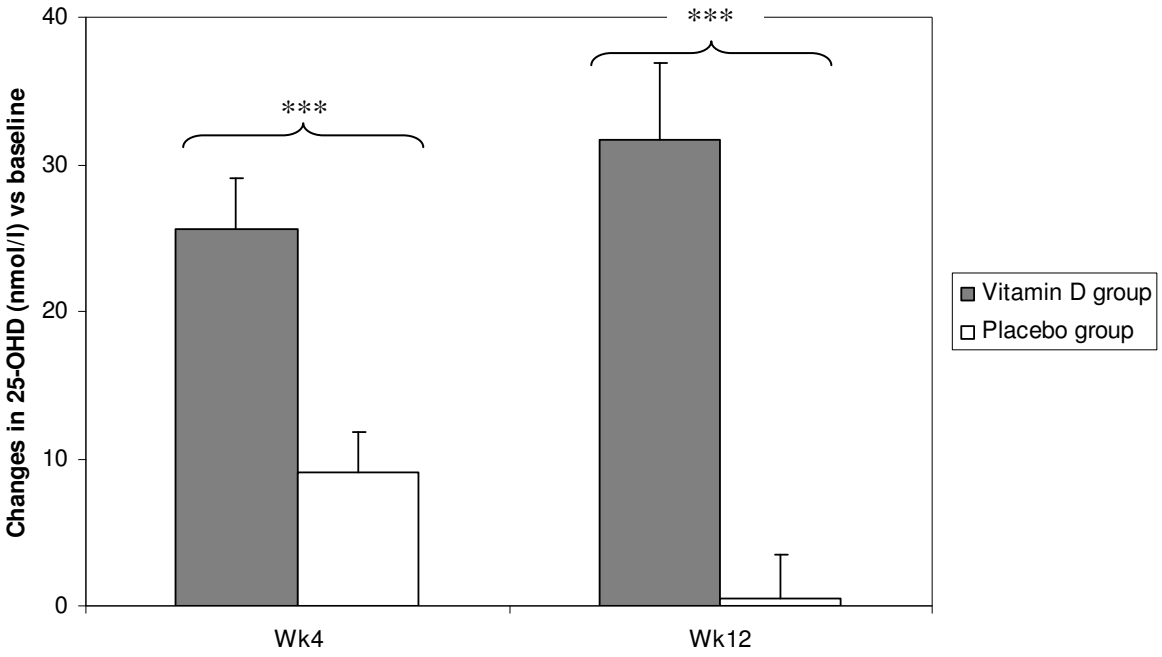

Figure 2: Changes in 25-hydroxycholecalciferol in vitamin D und placebo group after 4 and 12 weeks of intervention compared to baseline

Data are means ± SEM based on $n = 38$ (vitamin D group) and $n = 41$ (placebo group), respectively. Patients who adequately adhered to the protocol and who ingested at least 80% of target dose were included in this analysis. Asterisks indicate significant differences between the groups according to unpaired *t*-test ($P \leq 0.001$).

Discussion

To our knowledge, this is the first study investigating whether high-dose VD supplementation by an oily preparation leads to VD sufficiency (25-OHD ≥75 nmol/L) in obese patients 12 weeks after SG.

Supplementation of 80 µg/d (3,200 IU) VD_3 increased 25-OHD to 92 nmol/L (wk_{12}) (Table 2). These changes can be clearly ascribed to VD treatment as they were significantly higher compared to the placebo group (Figure 2). An increase in 25-OHD by other sources can be excluded as the total intake of VD by food and multivitamins (wk_3 5.6 µg/d, wk_{11} 5.7 µg/d; medians) was negligible. The lack of changes in 25-OHD in the placebo group (Table 2) does not indicate a postoperative increase in 25-OHD as observed in several [33, 34], but not all studies [35]. As polymorphisms of genes responsible for the transport and metabolism of VD strongly affect 25-OHD level [36], changes in 25-OHD after SG may be highly individual and may become evident in the long term.

25-OHD levels ≥ 75 nmol/L were achieved in 68.4% of the patients of the VD group; only a minority (2.6% in wk_4, 7.9% in wk_{12}) had still levels < 50 nmol/L (Table 3). This was not attained in studies supplementing less VD (20-50 µg/d) after SG [9, 15, 16]. Seemingly, such doses cannot prevent a VD deficiency in morbid obesity where the requirement is increased [11]. The high-dose of VD_3 supplied and the oily application form were probably decisive for the success of our intervention as the low fat intake by food after SG (wk_3 12 ± 1 g/d; wk_{11} 26 ± 1 g/d) may reduce the bioavailability of VD. Previous studies provided lower doses of VD by non-oily preparations (e.g., tablets) without recommendations to ingest the supplement together with fatty foods [9, 15].

191 nmol/L was the highest individual 25-OHD level observed at wk_{12} which was below the maximum safe level of 250 nmol/L [1]. Therefore, risks of VD hypervitaminosis by supplementation of 80 µg/d VD_3 can be excluded. Holick et al. recommend to supply even 150-250 µg/d (6,000-10,000 IU) VD in obese patients with VD deficiency and 75-150 µg/d (3,000-6,000 IU) to maintain VD sufficiency (1).

PTH was not affected by VD supplementation (Table 2). In healthy adults, changes in PTH have shown to depend on initial PTH level [37], which was above the cutoff value (> 6.5 pmol/L) in only 15.2% of the patients (Table 3). The increase in Ca_{corr} was only significant in the VD group, probably due to the improved VD status even if a treatment effect could not be observed by repeated measures ANOVA.

Cardiometabolic risk factors were not affected by VD supplementation (Table 4). This was surprising as the supplementation of a similar dose of VD_3 (83 µg/d) in overweight/obese patients reduced triglycerides and TNF-α in patients with VD deficiency [30]. Other studies found a VD-induced reduction of TNF-α [30, 38]. The high mean 25-OHD level of our patients at baseline compared to those of Zittermann et al. (60 vs. 30 nmol/L) and the lower levels of

TNF-α (2.6 pg/mL) compared to other studies (7.8 pg/mL [30]; 22.4 pg/mL [38]) may explain the lack of changes.

As expected, a time-dependent decrease in triglycerides, TC, and LDL occurred in both groups, which is in line with other findings [39, 40] and may result from weight loss (31.0 ± 8.0 kg within 12 weeks) after SG. In contrast to lipids, effects on glucose metabolism and on inflammation over time became only significant in the placebo group achieving lower values of glucose and HbA_{1c} at wk_{12} and of CRP at wk_4 than before SG (Table 4). The reason for this remains unclear. The prevalence of diabetes was not different between the groups. However, bias induced by changes in medical treatment cannot be excluded as it was not recorded.

One strength of our study was the use of on oily supplement which may increase VD bioavailability. Furthermore, the broad range of parameters related to VD deficiency provides a clear estimation on the impact of VD supplementation on VD status and on related parameters of mineral metabolism.

Initial 25-OHD level was higher than expected from the results of our own group [29] and others [9, 18, 41]. These, however, may reflect seasonal variations [42]. 94.9% of our patients were included between June and September when even obese patients in Switzerland had relatively high 25-OHD values and a low prevalence of VD deficiency [42]. An initial screening on 25-OHD was not feasible in our study and is not part of clinical practice, but should be done in future studies.

In conclusion, supplementation of 80 µg/d VD_3 by an oily preparation is an effective and safe measure to prevent VD deficiency and to achieve VD sufficiency in most obese patients 12 weeks after SG. The effect on cardiometabolic risk remains unclear and should be investigated in future studies taking into account the medical treatment.

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GENERAL DISCUSSION

The cross-sectional study (CHAPTER ONE) investigated the pro-/vitamin and mineral status and its association with micronutrient intake in obese patients preoperatively, with the focus being on vitamin D. Data on 25-OHD status was used to calculate the sample size for the interventional study (CHAPTER TWO), which investigated whether high-dose vitamin D supplementation by an oily preparation may prevent vitamin D deficiency or insufficiency, and may affect biochemical parameters related to mineral metabolism and cardiometabolic risk in these patients postoperatively.

The results of the cross-sectional study show that morbidly obese patients in Germany frequently suffer from micronutrient deficiencies before bariatric surgery, especially concerning vitamin D, ascorbic acid, and β-carotene (CHAPTER ONE, Table 2). Vitamin D deficiency is a public health issue [(1)], but not ascorbic acid and β-carotene [(2)]. Both serum/plasma levels and the intake of vitamin D, ascorbic acid, and β-carotene were below the corresponding cutoff values in many patients preoperatively (CHAPTER ONE, Tables 2 and 3). However, the low intake of these pro-/vitamins was not related to the poor status in serum/plasma. Thus, the low intake does not reflect an inadequate status (CHAPTER ONE, Table 4). These results are in contrast to the general population in Germany [(2)] and may be explained due to low intake, an increased requirement in antioxidants such as vitamin C and β-carotene owing to chronic inflammation, and an increased distribution volume in morbidly obese patients.

Vitamin D deficiency has been frequently observed in bariatric patients before surgery [(3-5)] and afterwards [(6-8)]. Consequences of vitamin D deficiency have been reported as severe clinical complications of bariatric surgery and include secondary hyperparathyroidism, hypocalcaemia, fractures, osteoporosis and skeletal mineralization defects [(9-12)]. Vitamin D deficiency (25-OHD levels < 50 nmol/L) was prevalent in 84% of patients of the present cross-sectional study (CHAPTER ONE, Table 2) and in 40.5% of the patients of the present interventional-study at baseline (CHAPTER TWO, Table 3), which is consistent with previous studies [(4, 13, 14)]. 23% of patients in the cross-sectional study (CHAPTER ONE, Table 2) and 15.2% (CHAPTER TWO, Table 3) of patients in the interventional study suffering from a vitamin D deficiency had evidence of secondary hyperparathyroidism, showing PTH levels > 6.5 nmol/L. These findings are also consistent with previous reports [(4, 15, 16)] and underline the risk of bariatric patients developing osteomalacia.

There are multiple reasons to explain vitamin D deficiency in obesity: 1) limited sun exposure [(17)], 2) decreased bioavailability of vitamin D from cutaneous and dietary sources due to sequestration in adipose tissue [(18)], and 3) inadequate vitamin D intake [(19)]. As obese patients are less responsive to UVB exposure [(17)], vitamin D supplementation before and after bariatric surgery is an important measure to improve vitamin D status. So far, only a few

studies have evaluated the appropriate vitamin D dose to prevent vitamin D deficiency after bariatric surgery. Most of them investigated patients after undergoing malabsorptive procedures and provided supplementation doses of 10-20 µg/d vitamin D (400-800 IU/d) [20-22]. Only a few prospective studies were performed in patients after SG. In these studies, daily supplementation of 20-22 µg vitamin D_3 (800-880 IU) was not sufficient to increase 25-OHD to levels > 50 nmol/L [23-25]. Interestingly, supplementation of 50 µg/d vitamin D_3 (2,000 IU) increased 25-OHD levels in obese patients 3 months after SG, but 25-OHD levels > 50 nmol/l were only seen in 73.9% of the patients [26]. Supplementation of 20 µg/d (800 IU) vitamin D increased serum 25-OHD > 50 nmol/L in 97.5% of healthy women (BMI 28.2 ± 6.5 kg/m^2) in a study of Gallagher et al., but the response to vitamin D supplementation was inversely related to body weight [27]. Therefore, bariatric patients may require more than 50 µg/d vitamin D to achieve 25-OHD levels > 50 nmol/L.

Recommendations concerning vitamin D and vitamin D supplementation after bariatric surgery are different in the literature and have been revised, especially in the past few years. In 2011, the US Endocrine Society`s Clinical Practice Guideline recommends 150–250 µg/d (6,000–10,000 IU/d) vitamin D in obese patients for the treatment of vitamin D deficiency and 75–150 µg/d (3,000–6,000 IU/d) vitamin D to maintain 25-OHD levels > 75 nmol/L [28]. In 2013, the American Association of Clinical Endocrinologists, the Obesity Society and the American Society for Metabolic and Bariatric Surgery (AACE/TOS/ASMBS) updated their Medical Guideline for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient from 2009. Instead of 10-20 µg/d (400–800 IU/d) vitamin D [29], they now recommend at least 75 µg/d (3,000 IU/d) to obtain 25-OHD levels > 75 nmol/L [30]. In a recently published study of Moore et al., supplementation of 50 µg/d (2,000 IU/d) for 3 months after SG led to 25-OHD levels of > 75 nmol/L in only 37% of the obese patients (BMI: 46.3 ± 8.1 kg/m^2) [26]. In the present interventional study, supplementation of 80 µg/d (3,200 IU/d) for 3 months after SG resulted to 25-OHD levels of > 75 nmol/L in at least 68% of the patients (BMI: 52.0 ± 12.1 kg/m^2). The recommendations published for vitamin D [30] include the analysis of 25-OHD levels in each bariatric patient pre- and postoperatively. However, this is often not feasible in clinical practice, as this investigation is not offered in each bariatric surgery center.

However, there is no consensus on the definition of *optimal* vitamin D status and on the definition of vitamin D deficiency [31], which reflects different goals and views on current evidence. The U.S. Endocrine Society defines vitamin D deficiency as 25-OHD levels less than 20 ng/mL (50 nmol/L), vitamin D insufficiency as 21–29 ng/mL (52.5–72.5 nmol/L) and vitamin D sufficiency as 30-100 ng/mL (75–250 nmol/L) [28]. Both, the U.S. Endocrine Society [28] and the AACE/TOS/ASMBS [30] suggested 25-OHD levels > 30 ng/mL (75 nmol/L) as the optimal level to maximize vitamin D´s beneficial effects, e.g. decreasing the risk for

developing osteoporosis. In contrast, the German, Austrian, and Swiss Nutrition Societies [32] refer to a cutoff value of 20 ng/mL (50 nmol/L) which is needed to minimize the risk of bone loss and secondary hyperparathyreoidism. Accordingly, the US Institute of Medicine [33] recommends to achieve a threshold of 20 ng/mL (50 nmol/L) to maintain skeletal health in 97.5% of the adult population. To achieve 50 nmol/L, the German, Austrian, and Swiss Nutrition Societies actually recommend 20 µg/d vitamin D for healthy subjects without endogenous vitamin D synthesis [32]. In the present interventional study, the vitamin D dosage was fourfold higher than the reference value of the German, Austrian, and Swiss Nutrition Societies, but it neither exceeded the upper tolerable intake for adults of 100 µg/d vitamin D set by the European Food Safety Authority (EFSA) [34] nor the maximum 25-OHD value of 250 nmol/L which is considered to be safe [28]. Furthermore, clinical symptoms of vitamin D hypervitaminosis did not occur. For these reasons, the supplementation of 80 µg/d vitamin D for 12 weeks after SG can be considered as a safe measure, which is effective to achieve 25-OHD levels > 50 nmol/L in nearly all patients and 25-OHD levels > 75 nmol/L in most patients, the latter being recommended of the AACE/TOS/ASMBS for the bariatric patient [30] (CHAPTER TWO).

The relatively low fat intake in the first 3 months after SG (wk_3 12 ± 7 g/d, wk_{11}: 26 ± 11 g/d) may reduce vitamin D absorption, suggesting that the postoperative use of an oily vitamin D preparation (Vigantol oil® diluted with Miglyol 812®) may be an ideal application form to ensure quantitative absorption of supplied vitamin D (CHAPTER TWO). However, the ideal application form of vitamin D used in supplements for patients after bariatric surgery has not been discussed yet. In previous studies, vitamin D tablets were used [23, 25, 35] or details on application forms were not reported [24]. Interestingly, Raimundo et al. showed recently that the mean increase in 25-OHD level after vitamin D supplementation was significantly larger when combined with a meal including at least 15 g of fat [36]. Recommendations to ingest more fat in the first three weeks after SG are only practicable to a limited extent due to reduced food intake [37]. Therefore, supplementation of vitamin D by oily preparations may be an ideal solution in the first 12 weeks after surgery to improve vitamin D absorption and vitamin D status. The question whether the oily application is decisive for the success of high-dose vitamin D supplementation should be investigated in further studies, comparing the effect of oily and non-oily vitamin D preparations on 25-OHD level.

Surprisingly, the patients of the present interventional study had much higher mean 25-OHD levels at baseline (59 ± 24 nmol/L; *n* = 79) (CHAPTER TWO, Table 2) compared to the patients of the cross-sectional study (35 ± 17 nmol/L; *n* = 43) (CHAPTER ONE, Table 2). The reasons for this observation remain speculative. In both studies, patients were consecutively included. Nearly all patients who were asked to participate in the cross-

sectional study were included. However, participation in this study requires only one single blood withdrawal and the completion of one single 3-d food record and a single questionnaire. In contrast, some patients who fulfilled the inclusion criteria refused to join the interventional study or dropped out throughout the study, possibly because of the relatively high efforts involved in participation. Consequently, most patients who were enrolled in the present interventional study were highly motivated. This is reflected by the excellent compliance with treatment (96%) (CHAPTER TWO). Highly motivated patients may take part in more outside activities which is suggested to increase both UVB exposure and endogenous 25-OHD synthesis [19]. This assumption is supported by the fact that the 15 patients of the interventional study who dropped out had a much lower mean 25-OHD level at baseline (43 ± 11 nmol/L) than the 79 patients who finished the study (59 ± 24 nmol/L). The high mean 25-OHD level of > 50 nmol/L in the patients of the present interventional study (CHAPTER TWO) shows that the patients were not deficient in vitamin D before SG. However, this may explain why parameters of mineral metabolism have not been improved and parameters of cardiometabolic risk have not been influenced by vitamin D supplementation in these patients (CHAPTER TWO).

In a previous study performed in Switzerland, 25-OHD levels in obese individuals have shown a marked seasonal variation [38] which are similar to those observed in the general population in Germany [1]. It may be important to mention that the patients of our cross-sectional study were enrolled between April and June and those of our interventional study between June and October. Because the cross-sectional study was conducted in spring, serum 25-OHD levels probably reflect mean vitamin D levels obtained throughout the year. In contrast, patients of the interventional study were initially investigated in summer/autumn, which may explain the distinctively higher 25-OHD levels in these patients. Ernst et al. [38] found a 3.8-fold higher prevalence for vitamin D deficiency in obese patients during the winter season (February–March) than in the summer season (August–September), which may underline the hypothesis.

Interestingly, several studies showed a postoperative increase in serum 25-OHD levels within six months after bariatric surgery [21, 39-41]. This observation suggests that vitamin D may be released from fat stores from initial weight loss. In the present interventional study, 25-OHD levels of the placebo group increased at baseline from 58 ± 4 nmol/L to 67 ± 5 nmol/L after 4 weeks, which, however, did not reach significance (CHAPTER TWO, Table 2). This was not observed in other studies, where no positive correlation between the amount of the postoperative weight loss and 25-OHD level has been found [42, 43]. The question if postoperative changes may simply reflect seasonal variations cannot be excluded. However, it is conceivable that vitamin D may be temporarily released from body fat during a phase of rapid weight loss in the first months after surgery, but this

does not lead to an adequate vitamin D status in the postoperative period when body fat is reduced. To clarify this hypothesis, larger prospective studies, which include information on seasonal variation, UVB exposure, and assessment of adipose tissue are needed.

Besides discussing the strategies of vitamin D supplementation after bariatric surgery, the question arises whether other micronutrients should be supplemented postoperatively. The intake of both retinol and tocopherol did not correlate with the corresponding status in plasma (CHAPTER ONE, Table 4). Concerning the nutritional intake, nearly half of the patients did not reach the reference values for nutritional intake of the German, Austrian, and Swiss Nutrition Societies [44] for retinol (55.8%) and for tocopherol (48.5%) (CHAPTER ONE, Table 3). This indicates an inadequate nutritional supply of these vitamins, which was not, however, reflected by the status in plasma. However, plasma retinol levels are regulated homeostatically and retinol may derive partly from provitamin A carotinoids, and plasma tocopherol levels are regulated by the hepatic tocopherol binding protein [45, 46].

The dietary intake of vitamin C and β-carotene in the cross-sectional study (vitamin C 55.8%, β-carotene 72.1%) (CHAPTER ONE, Table 3) was mostly below the current recommendations of the German, Austrian, and Swiss Nutrition Societies. Fruits and vegetables are known to be the major sources of these pro-/vitamins in Germany [47] and an intake of 5 portions of fruits and vegetables per day is recommended by the German Nutrition Society [48]. As a low intake of fruit and vegetables has been found in severe obesity [49], which is in accordance with our findings (CHAPTER ONE), an increased consumption of fruit and vegetables should be recommended preoperatively in nutritional consultations and should be specified in the corresponding guidelines. As the capacity of the patient's stomach is reduced postoperatively [50], these recommendations are not practicable and an adequate intake of the pro-/vitamins has to be solved in a different way.

Following bariatric surgery, expert recommendations and guidelines demand a life-long regimen of daily micronutrient supplementation [30]. However, its efficacy to prevent pro-/vitamin deficiencies, including those of ascorbic acid or β-carotene, has not been elucidated yet. Therefore, further investigations are needed to determine whether regular supplementation of multivitamins may postoperatively prevent micronutrient deficiencies. It should be mentioned that the compliance with multivitamin supplementation recommendation is different as some patients either do not understand the need, are concerned about the supposed high costs, or are uncertain by the large variety of commercial supplements [51]. It would also be interesting to investigate the efficacy of natural dietary approaches as an alternative to synthetic multivitamin preparations. For example, smoothies prepared from fruits and vegetables rich in vitamin C and β-carotene may be superior to multivitamin preparations as they may ensure an adequate supply of most critical vitamins, a range of

provitamin A carotinoids and other phytochemicals with antioxidant properties. It could be suggested that smoothies, due to their liquid consistence, may be better tolerated than fruits and vegetables, especially in the first months after surgery. Smoothies may be an interesting option for practical reasons as they are available in small amounts of 100 ml and ready-to-eat. The question if smoothies may be an efficient measure to ensure an adequate pro-/vitamin status in bariatric patients deserves further research.

Recent studies postulate that postoperative micronutrient deficiencies and most diet-related surgical complications could be prevented by investigating the preoperative micronutrient status and by developing tailoring of specific nutritional programs pre- and also postoperatively [8]. Some micronutrient complications are well known, including those relating to vitamin D, calcium, and iron deficiency, but the best strategies for prevention and treatment, have not been elucidated yet. To date, practitioners have had to rely on limited evidence when prescribing appropriate foods, dietary supplements, and procedure-specific nutritional recommendations [29]. As shown in the interventional study, oral supplementation of a fixed high-dose of 80 µg/d vitamin D by an oily preparation is an effective and safe measure to prevent vitamin D deficiency and to achieve vitamin D sufficiency in most patients (CHAPTER TWO), and may be recommended for clinical routine to the bariatric patient at least in the first 12 weeks after SG. However, for many other critical micronutrients, including vitamin C and β-carotene, awareness of a potential risk of deficiency is low and monitoring of these micronutrients will not be carried out. The lack of knowledge might strengthen nutritional complications in post-bariatric patients. Much more evidence on the basis of well-designed interventional studies is needed to specify nutritional recommendations to prevent and treat micronutrient deficiencies in these patients. Several guidelines for nutritional practice recommend routine monitoring of nutritional status in bariatric patients [30, 52]. Measurement of the preoperative micronutrient status will help supplement patients before and optimize nutritional therapy after surgery, but laboratory investigations of the whole spectrum of micronutrients in serum, blood or urine is expensive and not offered in each centre performing bariatric surgery. In conclusion, more research is required to specify the present evidence-based guidelines to improve nutritional and metabolic outcomes in the long-term care for the growing number of bariatric patients.

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ANNEX A: Questionnaire of the cross-sectional study

Studie: „Ernährungsstatus bei morbid-adipösen Patienten vor laparoskopischer Sleeve-Resection“

Patientennummer: _____ **Datum: _____**

Gewichtsverlauf

Körpergröße: _____ Aktuelles Gewicht: _____

Sie haben deutliches Übergewicht seit _____ Jahren.

Ihr Wunschgewicht liegt bei _____ kg.

Ihr höchstes Gewicht als Erwachsener war _____ kg, das war im Jahr _____

Ihr niedrigstes Gewicht als Erwachsener war _____ kg, das war im Jahr _____

Die bisher größte Gewichtsabnahme war _____ kg, das war im Jahr _____

Diätvorgeschichte

Ihre erste Diät haben Sie gemacht mit _____ Jahren.

Wie häufig haben Sie bereits Diäten durchgeführt?

□ noch nie □ 1-5 mal □ 5-10 mal □ > 10 mal □ regelmäßig (mind. 1 mal pro Jahr) □ ständig

Welche Diätversuche haben Sie bisher hinter sich?

□ Weight Watchers
□ Atkins
□ Optifast
□ Trennkost
□ Nulldiät
□ Verschiedene (Kohlsuppendiät, Brigitte-Diät, Figura-Fit, etc.)
□ Xenical/Reductil
□ Pulverdiäten (z.B. BCM, Slim Fast)
□ Herbalife
□ Sonstiges: _____

Hatten Sie bereits einen Kuraufenthalt zur Gewichtsreduktion? □ ja □ nein

Wo?, Wann? Dauer der Kur?, Gewichtsreduktion? _____

_____

Hatten Sie bereits eine qualifizierte Ernährungsberatung (Einzel-/Gruppenberatung)?

□ nein □ ja, _____

_____

Gibt es Versuche der Gewichtsreduktion, bei der Sie mehr als 5 kg abgenommen haben?

	Versuch der Gewichtsreduktion	**Jahr**	**Zeitraum**	**Gewichtsverlust**
1				
2				
3				

Wenn Sie wieder zugenommen haben, was waren aus Ihrer Sicht die Gründe dafür?

□ Stress

□ Frustration

□ fehlendes Sättigungsgefühl

□ familiäre Probleme

□ kein Durchhaltevermögen

□ Sonstiges:

_____

Warum möchten Sie abnehmen?

_____

_____

Krankengeschichte

Welche Medikamente nehmen Sie ein?

□ ASS

□ Medikamente gegen Bluthochdruck: _____

□ Marcumar

□ Insulin (Einheiten pro Tag): _____

□ Antidiabetika: _____

□ Sonstige: _____

_____

Sind in Ihrer Familie nennenswerte Vorerkrankungen bekannt? □ nein □ ja,

_____

Wer aus Ihrer Familie leidet unter massivem Übergewicht? (z.B. Eltern, Kinder, Geschwister, Tanten, Onkel, etc.)

_____

Wie oft haben Sie Sodbrennen? □ nie □ gelegentlich □ täglich

Leiden Sie an einer dieser Erkrankungen?

□ Diabetes
□ Asthma
□ Herzerkrankung
□ Bluthochdruck
□ Nierenerkrankung
□ Lungenerkrankung
□ Gicht
□ Schilddrüsenüberfunktion
□ Schilddrüsenunterfunktion
□ Schlafapnoe
□ Lebererkrankung
□ Gallensteine
□ Rheuma/Rheumatische Erkrankungen
□ Sonstige:

_____

_____

Haben Sie Arthrose? □ nein □ ja, seit _____

Hatten Sie schon einen Bandscheibenvorfall? □ nein □ ja, im Jahr _____

Hatten Sie bereits Voroperationen (speziell im Bauchraum)? □ nein □ ja,

_____

_____

Befinden Sie sich in orthopädischer Behandlung? □ nein □ ja, seit _____

Haben Sie Schmerzen im Bereich der ..... ?

□ Wirbelsäule
□ Hüfte
□ Kniegelenke
□ Sprunggelenke
□ Füße

Lebensstil und Essverhalten

Rauchen Sie? □ nein □ ja, _____Zigaretten/Tag.

Ex-Raucher seit _____.

Wie oft trinken Sie Alkohol? □ nie □ 1 x/Jahr □ 1 x/Monat □ 1x/Woche □ täglich

Hatten Sie schon einmal Probleme mit dem Alkoholkonsum oder dem Konsum anderer Drogen? □ nein □ ja

Welchen Beruf üben Sie aus?

_____

Arbeiten Sie im Schichtdienst? □ nein □ ja

Wie oft treiben Sie Sport? □ nie □ 1 x/Monat □ 1x/Woche
□ 2 x/Woche □ täglich

Welchen Sport treiben Sie?

_____

_____

Wieviel Zeit verbringen Sie pro Tag ungefähr außer Haus? _____ Minuten

Gibt es bei Ihnen regelmäßige Mahlzeiten? □ ja □ nein
Essen Sie besonders große Portionen? □ ja □ nein

Verzehren Sie mehr als 3 Mahlzeiten pro Tag? □ ja □ nein
Kochen Sie selbst zu Hause? □ ja □ nein
Wie oft essen Sie Fleisch/Wurst? □ häufig □ selten □ nie
Wie oft essen Sie Süßigkeiten? □ häufig □ selten □ nie
Welche Süßigkeiten mögen Sie am liebsten? _____

_____

Was trinken Sie am Tag?

_____

_____

Welche Menge trinken Sie am Tag? _____

Leiden Sie unter Essattacken? □ ja □ nein

Waren Sie schon einmal in psychologischer Behandlung? □ ja □ nein

Leiden Sie unter Depressionen? □ ja □ nein

Werden Sie derzeit aufgrund Ihrer Depressionen behandelt? □ ja □ nein

Allgemeines

Wie sind Sie über die Möglichkeit einer chirurgischen Maßnahme zur Gewichtsreduktion aufmerksam geworden?

□ Fernsehen □ Selbsthilfegruppen
□ Ärztliche Beratung □ Zeitung
□ Krankenkasse □ Internet
□ Sonstiges: _____

Wie haben Sie sich über chirurgische Maßnahmen zur Gewichtsreduktion kundig gemacht?

□ ich habe mich bereits weiter informiert über

□ Fernsehen □ Selbsthilfegruppen
□ Ärztliche Beratung □ Zeitung
□ Krankenkasse □ Internet
□ Sonstiges: _____

Wir bedanken uns für Ihre Mitarbeit!

ANNEX B: Patient information of the cross-sectional study

Studie „Ernährungsstatus bei morbid-adipösen Patienten vor laparoskopischer Sleeve-Resection“

Sehr geehrte Patientin, sehr geehrter Patient,

zur genaueren Erfassung des Ernährungsstatus bei morbid-adipösen Patienten vor laparoskopischer Sleeve-Resection ist eine wissenschaftliche Untersuchung am Menschen erforderlich. Die o.g. Studie wird vom Klinikum Vest in Kooperation mit dem Institut für Ernährungs- und Lebensmittelwissenschaften der Universität Bonn durchgeführt nach Beratung durch die Ethikkommission der Universität Bonn und der Ethikkommission der Ärztekammer Westfalen-Lippe und der Universität Münster. Die Teilnahme ist freiwillig. Selbstverständlich müssen Sie keine Nachteile befürchten, wenn Sie an der Studie nicht teilnehmen oder Ihre Einwilligung widerrufen.

Hintergrund
Seit Juni 2010 ist die laparoskopische Schlauchmagen-Bildung in der Leitlinie „Chirurgie der Adipositas“ der Deutschen Gesellschaft für Allgemein- und Viszeralchirurgie im Rahmen der Adipositastherapie als eigenständiges Verfahren in der Adipositaschirurgie anerkannt. Es gibt jedoch Hinweise, dass ein sekundärer Hyperparathyreodismus – eine Störung der Nebenschilddrüsenfunktion – dadurch vermehrt auftritt, was durch einen Vitamin D Mangel begünstigt wird. Vermutlich liegt dieser bereits vor der Operation vor. Möglicherweise geht der Mangel an Vitamin D auch mit anderen Vitaminmängeln einher.

Studienziel
Primäres Ziel der geplanten Untersuchung ist es, den Vitamin D Status bei Patienten zu untersuchen, die sich einer Schlauchmagen-Bildung unterziehen. Diese Daten ermöglichen die Berechnung der erforderlichen Teilnehmerzahl für eine spätere Studie, die zeigen soll, ob die Einnahme von Vitamin D und Calcium das Risiko, eine Störung der Nebenschilddrüsenfunktion zu entwickeln, senkt. Diese Berechnung ist für eine vernünftige Studienplanung unerlässlich. Ein weiteres Ziel ist die Bestimmung des Vitamin-Status im Blut dieser Patienten.

Studienablauf
Im Rahmen der Routineuntersuchung vor dem operativen Eingriff werden zusätzlich zur normalen Blutabnahme 2 Röhrchen Blut entnommen (insgesamt etwa 16 ml). Damit soll die Konzentration von spezifischen Vitaminen (Vitamin A, C, D, E) und Mineralstoffen (Calcium, Magnesium, Phosphat) bestimmt werden. Darüber hinaus werden Substanzen gemessen, die zur Beurteilung der Ernährungssituation des Patienten benötigt werden.
Diese Blutmenge ist unbedenklich. Die Blutentnahme erfolgt im Rahmen einer routinemäßig durchgeführten Blutentnahme vor Durchführung der Operation. Es entstehen daher keine zusätzlichen Risiken durch die Blutabnahme. Außerdem wird die Energie– und Nährstoffzufuhr anhand eines 3-Tages Ernährungsprotokolls eingeschätzt.

Wichtiger Hinweis
Sie können an der Studie teilnehmen, wenn Sie,

- **10 Tage vor der ersten Blutentnahme keine Nahrungsergänzungsmittel einnehmen d.h. Multivitaminpräparate**
- nicht schwanger sind oder stillen
- zwischen 18 und 65 Jahre alt sind
- bereits an keiner anderen klinischen Prüfung teilnehmen
- keine Voroperationen am Magen haben

- gemäß der Leitlinie „Chirurgie der Adipositas“ alle Einschlusskriterien für eine adipositas-chirurgische Operation erfüllen

Durch die Teilnahme an der Studie leisten Sie einen wertvollen Beitrag, um die Versorgung mit bestimmten Mikronährstoffen bei Patienten mit morbider Adipositas einschätzen zu können. Außerdem ermöglicht Ihre Teilnahme die professionelle Planung eines weiteren Projekts, welches die notwendigen Daten liefert, um wissenschaftlich basierte Ernährungsempfehlungen bei Patienten mit einer Schlauchmagen-Bildung definieren zu können.
Ihre Daten werden pseudonymisiert. Sollten Sie weitere Fragen haben, können Sie sich jederzeit an uns wenden.

Ihre Ansprechpartner für Rückfragen

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ANNEX C: Questionnaire of the interventional study

Studie: „Prävention von Hypocalcämie, Vitamin D Mangel und sekundärem Hyperparathyreodismus bei Patienten nach laparoskopischer Sleeve-Gastrektomie durch Supplementierung von Vitamin D?“

Probandennummer: _____ **Datum: _____**

Gewichtsverlauf

Körpergröße: _____ Aktuelles Gewicht: _____

Sie haben deutliches Übergewicht seit _____ Jahren.

Ihr Wunschgewicht liegt bei _____ kg.

Diätvorgeschichte

Ihre erste Diät haben Sie gemacht mit _____ Jahren.

Wie häufig haben Sie bereits Diäten durchgeführt? □ noch nie

□ 1-5 mal □ 5-10 mal □ > 10 mal □ regelmäßig (mind. 1 mal pro Jahr) □ ständig

Welche Diätversuche haben Sie bisher hinter sich?

□ Weight Watchers
□ Atkins
□ Optifast
□ Trennkost
□ Nulldiät
□ Xenical/Reductil
□ Pulverdiäten (z. B. BCM, Slim Fast)
□ Herbalife
□ Verschiedene (Kohlsuppendiät, Brigitte-Diät, Figura-Fit, etc.)
□ Sonstiges: _____

Hatten Sie bereits eine qualifizierte Ernährungsberatung (Einzel-/Gruppenberatung)?

□ nein □ ja, bei

_____

Gibt es Versuche der Gewichtsreduktion, bei der Sie mehr als 5 kg abgenommen haben?

	Versuch der Gewichtsreduktion	**Jahr**	**Zeitraum**	**Gewichtsverlust**
1				
2				
3				

Wenn Sie wieder zugenommen haben, was waren aus Ihrer Sicht die Gründe dafür?

□ Stress
□ Frustration
□ kein Durchhaltevermögen
□ familiäre Probleme
□ fehlendes Sättigungsgefühl
□ Sonstiges: _____

Krankengeschichte

Welche Medikamente nehmen Sie ein?

□ ASS
□ Marcumar
□ Antidiabetika:
□ Blutdrucksenker: _____
□ Insulin (Einheiten pro Tag): _____
_____
□ Sonstige: _____
_____

Wer aus Ihrer Familie leidet unter massivem Übergewicht? (z.B. Eltern, Kinder, Geschwister, Tanten, Onkel, etc.)

_____

Wie oft haben Sie Sodbrennen? □ nie □ gelegentlich □ täglich

Leiden Sie an einer dieser Erkrankungen?

□ Diabetes
□ Asthma
□ Herzerkrankung
□ Nierenerkrankung
□ Schilddrüsenüberfunktion
□ Schilddrüsenunterfunktion
□ Bluthochdruck
□ Lungenerkrankung
□ Gallensteine
□ Schlafapnoe
□ Lebererkrankung
□ Gicht
□ Rheumatische Erkrankungen
□ Sonstige:

_____

Haben Sie Arthrose? □ nein □ ja, seit _____

Hatten Sie schon einen Bandscheibenvorfall? □ nein □ ja, im Jahr _____

Befinden Sie sich in orthopädischer Behandlung? □ nein □ ja, seit _____

Haben Sie Schmerzen im Bereich der ..... ?

□ Wirbelsäule
□ Hüfte
□ Sprunggelenke
□ Füße
□ Kniegelenke

Leiden Sie unter Depressionen? □ ja □ nein

Werden Sie derzeit aufgrund von Depressionen behandelt? □ ja □ nein

Lebensstil

Rauchen Sie? □ nein □ ja, _____Zigaretten/Tag.

Ex-Raucher seit _____.

Wie oft trinken Sie Alkohol? □ nie □ 1 x/Jahr □ 1 x/Monat
□ 1x/Woche □ täglich

Hatten Sie schon einmal Probleme mit dem Alkoholkonsum oder dem Konsum anderer Drogen?□ nein □ ja

Welchen Beruf üben Sie aus?

_____

Arbeiten Sie im Schichtdienst? □ nein □ ja

Wie oft treiben Sie Sport? □ nie □ 1 x/Monat □ 1x/Woche
□ 2 x/Woche □ täglich

Welchen Sport treiben Sie?

_____

Wieviel Zeit verbringen Sie pro Tag ungefähr außer Haus? (z.B. auf der Arbeit, beim Spazierengehen mit dem Hund, beim Einkaufen, etc.) _____ Minuten

Wieviel Zeit verbringen Sie pro Tag im Freien? _____Minuten.

Essverhalten

Gibt es bei Ihnen regelmäßige Mahlzeiten? □ ja □ nein

Verzehren Sie mehr als 3 Mahlzeiten pro Tag? □ ja □ nein

Kochen Sie selbst zu Hause? □ ja □ nein

Wie oft essen Sie Fleisch/Wurst? □ häufig □ selten □ nie

Wie viele Portionen Obst essen Sie pro Tag? □ max. 1 □ 2 □ 3 □ 4 □ 5 □ >5

Wie viele Portionen Gemüse essen Sie pro Tag? □ max. 1 □ 2 □ 3 □ 4 □ 5 □ >5

Wie oft essen Sie Süßigkeiten? □ häufig □ selten □ nie

Wie oft trinken Sie Milch, essen Milchprodukte und Käse?

□ täglich □ mehrmals täglich □ 1 x/Woche □ nie

Wie oft verzehren Sie Fettfisch (z.B. Hering, Makrele, Lachs)?

□ mind. 1x/Woche □ mind. 1x/Monat □ nie

Welche Flüssigkeitsmenge trinken Sie am Tag? _____

Welche Getränke trinken Sie am Tag? _____

Nehmen Sie regelmäßig Nahrungsergänzungsmittel ein (z.B. Vitamin C Tabletten oder Multivitaminpräparate?) □ ja □ nein

Wenn ja, welche? (evtl. Marke nennen)

Wenn ja, wie häufig? _____

Leiden Sie unter Essattacken? □ ja □ nein

Wir bedanken uns für Ihre Mitarbeit!

ANNEX D: Patient information of the interventional study

Studie: „Prävention von Hypocalcämie, Vitamin D Mangel und sekundärem Hyperparathyreodismus bei Patienten nach laparoskopischer Sleeve-Gastrektomie durch Supplementierung von Vitamin D?“

Sehr geehrte Patientin, sehr geehrter Patient,

zur genaueren Erfassung der Vitamin D-Versorgung bei morbid-adipösen Patienten vor und nach laparoskopischer Schlauchmagen-Bildung ist eine wissenschaftliche Untersuchung am Menschen erforderlich. Die o.g. Studie wird vom Klinikum Vest in Kooperation mit dem Institut für Ernährungs- und Lebensmittelwissenschaft der Universität in Bonn, dem Universitätsklinikum Bonn sowie dem Fachbereich Oecotrophologie der Hochschule Niederrhein durchgeführt. Die Teilnahme ist freiwillig. Selbstverständlich müssen Sie keine Nachteile befürchten, wenn Sie an der Studie nicht teilnehmen oder Ihre Einwilligung widerrufen.

Hintergrund
Seit Juni 2010 ist die laparoskopische Schlauchmagen-Bildung in der Leitlinie „Chirurgie der Adipositas“ der Deutschen Gesellschaft für Allgemein- und Viszeralchirurgie im Rahmen der Adipositasbehandlung als eigenständiges Verfahren in der Adipositaschirurgie anerkannt. Es gibt jedoch Hinweise, dass eine Störung der Nebenschilddrüsenfunktion (sekundärer Hyperparathyreodismus) dadurch vermehrt auftritt, was durch einen Vitamin D Mangel begünstigt wird. Wir konnten mit Hilfe einer vorhergehenden Studie herausfinden, dass 86 % unserer Patienten vor einer Schlauchmagen-Operation einen Vitamin D Mangel aufweisen. Wir vermuten nun, dass sich dieser nach dem Eingriff noch verstärken und somit eine Störung der Nebenschilddrüsenfunktion begünstigen kann.

Studienziel
Primäres Ziel der geplanten Untersuchung ist es zu untersuchen, ob man durch die tägliche Einnahme von Vitamin D nach Schlauchmagen-Bildung das Risiko eines Vitamin D-Mangels senken sowie eine Störung der Nebenschilddrüsenfunktion verhindern kann.

Weiterhin soll untersucht werden, ob durch eine tägliche Einnahme von Vitamin D nach Schlauchmagen-Bildung Risikofaktoren für Herzkreislauferkrankungen verbessert werden können und ob durch die generelle Empfehlung zur Einnahme eines Multivitaminpräparats postoperativ eine ausreichende Versorgung mit Vitaminen und Mineralstoffen sichergestellt werden kann.

Studienablauf
Die gesamte Studiendauer beträgt 12 Wochen. Während dieser Zeit erfolgen drei Blutuntersuchungen im Rahmen der klinischen Routineuntersuchungen vor der Operation sowie 4 und 12 Wochen nach der Operation. Es werden Ihnen zusätzlich zur normalen Blutabnahme 4 Röhrchen Blut entnommen (insgesamt etwa 14,8 ml). Damit soll die Konzentration von spezifischen Vitaminen (Vitamin A, C, D und E) und Mineralstoffen (Calcium, Magnesium, Phosphat) bestimmt werden. Darüber hinaus werden Substanzen gemessen, die zur Beurteilung der Ernährungssituation des Patienten benötigt werden.
Die zusätzliche Entnahme von 14,8 ml Blut ist unbedenklich. Die Blutentnahme erfolgt im Rahmen einer routinemäßig durchgeführten Blutentnahme. Es entstehen daher keine zusätzlichen Risiken. Außerdem wird die Energie– und Nährstoffzufuhr anhand eines 3-Tages Ernährungsprotokolls vor Studienbeginn sowie nach 4 und 12 Wochen eingeschätzt.

Im Rahmen dieser Studie erhalten Sie von uns über einen Zeitraum von 12 Wochen ein Vitamin D- oder ein Placebo-Präparat. Als Placebo wird ein Präparat bezeichnet, das frei ist von dem Wirkstoff, in dem Fall also frei von Vitamin D. Die Einteilung in die Vitamin D- oder Placebo-Gruppe erfolgt zufällig. Es handelt sich hierbei um eine doppelblinde Studie, d.h. weder Sie noch die Mitarbeiter des Adipositaszentrums wissen, ob Sie das Vitamin D- oder das Placebo-Präparat erhalten. Die Zuordnung wird erst zum Ende der Studie preisgegeben, um die Wirksamkeit der Vitamin D Gabe bewerten zu können. Durch die „doppelte Verblindung“ werden sehr aussagefähige Ergebnisse sichergestellt.

Vitamin D-Supplementierung
Teilnehmer der Vitamin D-Gruppe nehmen täglich 80 µg Vitamin D zu sich. Es handelt sich hierbei um eine Dosierung, die die täglich tolerierbare Höchstmenge für die Vitamin D Zufuhr von 100 µg Vitamin D nicht übersteigt. Auch bei einer zusätzlichen Vitamin D-Zufuhr aus Lebensmitteln sowie aus einem Multivitaminpräparat ist hier nicht mit gesundheitsschädlichen Effekten zu rechnen.

Hinweise zur Einnahme des Präparats

Bitte nehmen Sie **täglich 1 Einzeldosisbehälter** des Präparats mit einer fettreicheren Mahlzeit ein (in der ersten 4 Wochen nach Operation z.B. Quark, fettreichere Suppe; ab Woche 4 nach Operation z.B. Brot mit Käse oder Wurst, Fisch, Eintopf).
Sie können selbst wählen, ob Sie dies beim Frühstück, Mittagessen oder Abendessen tun. Das Präparat ist geschmacksneutral, so dass Sie keine Geschmacksveränderungen bemerken werden.

Bei dem Vitamin D haltigen Präparat handelt sich um ein sehr konzentriertes Präparat aus der Zentralapotheke des Knappschaftskrankenhauses Bochum. Daher bitten wir Sie die Einnahmevorschriften einzuhalten, da bei einer unsachgemäßen Anwendung (z. B. Nebenwirkungen infolge einer Überdosierung von Vitamin D) nicht ausgeschlossen werden können.

Falls Sie versehentlich eine Einnahme vergessen haben, fahren Sie am nächsten Tag wie gewohnt mit der Einnahme fort. Wir bitten Sie nur das Datum der vergessenen Einnahme für uns zu notieren.

Die ausgehändigten Tütchen mit Einzeldosisbehältern (pro Woche 1 Tüte) reichen für 12 Wochen aus. Bitte bringen Sie nach 12 Wochen die leeren Tüten im Rahmen Ihrer Nachsorgeuntersuchung mit.

Empfehlung zur Einnahme eines Multivitaminpräparates
Ausserdem empfehlen wir allen Teilnehmern die Einnahme eines Multivitaminpräparates (z.B. Centrum A-Z, Pfizer Consumer Healthcare GmbH, Berlin), weil man davon ausgehen kann, dass eine ausreichende Versorgung mit sämtlichen lebensnotwendigen Nährstoffen allein über den Lebensmittelverzehr wahrscheinlich nicht sichergestellt wird.

Teilnahmebedingungen
Sie können an der Studie teilnehmen, wenn Sie,

- **10 Tage vor der ersten Blutentnahme keine Nahrungsergänzungsmittel einnehmen d.h. Multivitaminpräparate**
- nicht schwanger sind oder stillen
- zwischen 18 und 65 Jahre alt sind
- nicht an einer anderen klinischen Prüfung teilnehmen
- keine Voroperationen am Magen haben
- keine Nierensteine haben
- Keine bekannte Hypercalcämie, d.h. erhöhte Calcium-Spiegel im Blut haben

- gemäß der Leitlinie „Chirurgie der Adipositas“ alle Einschlusskriterien für eine adipositas-chirurgische Operation erfüllen

Durch die Teilnahme an der Studie leisten Sie einen wertvollen Beitrag, um die Versorgung mit Vitamin D bei Patienten mit morbider Adipositas einschätzen zu können.

Ihre Daten werden pseudonymisiert, d.h. Ihr Name wird auf sämtlichen Dokumenten (z.B. Ernährungsprotokoll) sowie auf dem Probenmaterial durch eine Zahl ersetzt, um damit eine Identifizierung praktisch ausschließen zu können. Einige Blutparameter werden direkt im Labor des Klinikum Vest in Recklinghausen gemessen. Bei den restlichen Blutparametern erfolgt die Analytik zu einem späteren Zeitpunkt durch Mitarbeiter des Instituts für Ernährungs- und Lebensmittelwissenschaften in Bonn bzw. durch das Zentrallabor des Universitätsklinikum Bonn. Diese Blutproben werden im Labor des Klinikum Vest zwischengelagert und in Abständen nach Bonn transportiert. Wenn die Analysen abgeschlossen sind, wird das Probenmaterial vernichtet.

Sollten Sie weitere Fragen haben, können Sie sich jederzeit an uns wenden.

Ihre Ansprechpartner für Rückfragen

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ANNEX E: Food record of the interventional study

Studie: „Prävention von Hypocalcämie, Vitamin D Mangel und sekundärem Hyperparathyreodismus bei Patienten nach laparoskopischer Sleeve-Gastrektomie durch Supplementierung von Vitamin D?“

Allgemeine Hinweise zum Ernährungsprotokoll

1. Bitte führen Sie an folgenden Terminen ein Ernährungsprotokoll:
   - nach Ihrem Aufklärungsgespräch
   - 4 Wochen nach OP
   - 3 Monate nach OP

   Das Ernährungsprotokoll führen Sie ***jeweils über drei Tage***. Bitte bringen Sie das von Ihnen ausgefüllte Ernährungsprotokoll beim nächsten Nachsorgetermin mit.

2. Notieren Sie alle Speisen (Hauptmahlzeiten und Zwischenmahlzeiten) und Getränke, die Sie zu sich nehmen. Nehmen Sie bitte Ihr Ernährungsprotokoll überall mit hin, damit Sie die verzehrten Lebensmittel möglichst rasch dokumentieren und nichts vergessen wird.

3. Bitte geben Sie jeweils den Fettgehalt der verzehrten Nahrungsmittel an, z.B. „fettarmer Joghurt, 1,5 % Fett“, „Edamer 40 % Fett i. Tr.“ oder „Leerdamer light 32 % Fett i.Tr.“

4. Wenn Sie Fisch verzehren bitten wir Sie, die Art zu notieren (z.B. Scholle, Hering, Seelachs oder Lachs), weil der Vitamin D Gehalt sehr unterschiedlich ist. Das gilt auch für Margarine und Multivitaminsäfte. Bitte geben Sie für diese Produkte auch die die Marke an.

5. Bitte benutzen Sie zur Darstellung der Portionsgrößen haushaltsübliche Maße, wie z.B. 1 Tasse (200 ml) Tee, 1 EL (Esslöffel) Öl, 1 TL (Teelöffel) Zucker, etc.

6. Bei verpackten Lebensmitteln entnehmen Sie die verzehrte Menge den Angaben auf der Verpackung. Die übrigen Lebensmittel können Sie entweder wiegen, z. B. 60 g Kürbiskernbrot oder sie versuchen die Menge exakt zu beschreiben, z. B. ein handtellergroßes Schweineschnitzel bzw. eine hühnereigroße Kartoffel etc.

7. Beschreiben Sie die Zubereitungsart der Speisen, z. B. gegrillt, gekocht, gedünstet usw.

Ernährungsprotokoll Nr. _____
(nach Aufklärungsgespräch, nach 3 Wochen OP, 11 Monate nach OP)

Probandennummer:

Tag 1 / Datum: _____

Uhrzeit	Menge	Art des Lebensmittels, einschl. Getränke

Welches Wasser trinken Sie? Marke: _____

Mussten Sie heute erbrechen? _____

Welche Lebensmittel haben Sie nicht vertragen? _____

Sonstige Anmerkungen: _____

ANNEX F: Diary of Supplementation

Patiententagebuch zur Studie „Prävention von Hypocalcämie, Vitamin D Mangel und sekundärem Hyperparathyreodismus bei Patienten nach laparoskopischer Sleeve-Gastrektomie durch Supplementierung von Vitamin D?“

Sehr geehrter Studienteilnehmer,

um die Wirksamkeit der Maßnahme korrekt zu beurteilen ist es für uns wichtig zu wissen, ob Sie das Präparat in der vorgeschriebenen Menge (1 Behälter pro Tag) regelmäßig eingenommen haben. Bitte tragen Sie bei jedem Studientag das Datum ein. Wenn die Einnahme nach Vorschrift erfolgte, schreiben Sie in das jeweilige Kästchen bitte „ok“. Sollten Sie die Einnahme vergessen, notieren Sie das bitte im Protokoll, und fahren Sie am nächsten Tag wie gewohnt. Sollte eine Einnahme aus anderen Gründen einmal nicht möglich sein (z.B. aufgrund von Übelkeit), dann geben Sie das bitte in der nachfolgenden Tabelle an.

Woche 1	Tag 1 Datum:	Tag 2 Datum:	Tag 3 Datum:	Tag 4 Datum:	Tag 5 Datum:	Tag 6 Datum:	Tag 7 Datum:
Woche 2	Tag 8 Datum:	Tag 9 Datum:	Tag 10 Datum:	Tag 11 Datum:	Tag 12 Datum:	Tag 13 Datum:	Tag 14 Datum:
Woche 3	Tag 15 Datum:	Tag 16 Datum:	Tag 17 Datum:	Tag 18 Datum:	Tag 19 Datum:	Tag 20 Datum:	Tag 21 Datum:
Woche 4	Tag 22 Datum:	Tag 23 Datum:	Tag 24 Datum:	Tag 25 Datum:	Tag 26 Datum:	Tag 27 Datum:	Tag 28 Datum:

Woche 5	Tag 29 Datum:	Tag 30 Datum:	Tag 31 Datum;	Tag 32 Datum:	Tag 33 Datum:	Tag 34 Datum:	Tag 35 Datum:
Woche 6	Tag 36 Datum:	Tag 37 Datum:	Tag 38 Datum:	Tag 39 Datum:	Tag 40 Datum:	Tag 41 Datum:	Tag 42 Datum:
Woche 7	Tag 43 Datum:	Tag 44 Datum:	Tag 45 Datum:	Tag 46 Datum:	Tag 47 Datum:	Tag 48 Datum:	Tag 49 Datum:
Woche 8	Tag 50 Datum:	Tag 51 Datum:	Tag 52 Datum:	Tag 53 Datum:	Tag 54 Datum:	Tag 55 Datum:	Tag 56 Datum:
Woche 9	Tag 57 Datum:	Tag 58 Datum:	Tag 59 Datum:	Tag 60 Datum:	Tag 61 Datum:	Tag 62 Datum:	Tag 63 Datum:
Woche 10	Tag 64 Datum:	Tag 65 Datum:	Tag 66 Datum:	Tag 67 Datum:	Tag 68 Datum:	Tag 69 Datum:	Tag 70 Datum:
Woche 11	Tag 71 Datum:	Tag 72 Datum:	Tag 73 Datum:	Tag 74 Datum:	Tag 75 Datum:	Tag 76 Datum:	Tag 77 Datum:
Woche 12	Tag 78 Datum:	Tag 79 Datum:	Tag 80 Datum:	Tag 81 Datum:	Tag 82 Datum:	Tag 83 Datum:	Tag 84 Datum:

ANNEX G: Follow-up questionnaire

Follow-Up Fragebogen zur Studie

„Prävention von Hypocalcämie, Vitamin D Mangel und sekundärem Hyperparathyreodismus bei Patienten nach laparoskopischer Sleeve-Gastrektomie durch Supplementierung von Vitamin D?“

Probandennummer: _____ **Datum: _____**

Follow-Up 4 Wochen: □ Follow-Up 3 Monate: □

Aktuelles Gewicht: _____

Einnahme des Vitamin D-Präparats

Haben Síe das empfohlene Nahrungsergänzungsmittel eingenommen? □ ja □ nein

Wenn ja, wie häufig? □ täglich 1 Einzeldosisbehälter □ _____

Wie häufig haben Sie vergessen das Vitamin D-Präparat einzunehmen? _____

Einnahme des Multivitamin-Präparats

Haben Sie auch das empfohlene Multivitamin-Präparat eingenommen (Centrum A-Z, Pfizer Consumer Healthcare GmbH, Berlin)? □ ja □ nein

Wenn ja, wie häufig? □ täglich 1 x □1 x/Woche □ 3 x/Woche □ mehrmals täglich

Wenn nein, haben Sie ein anderes Multivitamin-Präparat eingenommen?

□ ja □ nein Wenn ja, welches? _____

Wenn ja, wie häufig? □ täglich 1 x □1 x/Woche □ 3 x/Woche □ mehrmals täglich

Nehmen Sie noch zusätzliche Nahrungsergänzungsmittel ein? (z.B. Zink, Biotin, Magnesium, etc.?) _____

Postoperatives Essverhalten:

Gibt es bei Ihnen regelmäßige Mahlzeiten? □ ja □ nein

Verzehren Sie mehr als 3 Mahlzeiten pro Tag? □ ja □ nein

Wie oft trinken Sie Milch, essen Milchprodukte und Käse?

□ täglich □ mehrmals täglich □ 1 x/Woche □ nie

Wie oft verzehren Sie Fettfisch (z.B. Hering, Makrele, Lachs)?

□ mind. 1x/Woche □ mind. 1x/Monat □ nie

Welche Flüssigkeitsmenge trinken Sie am Tag? _____

Welche Getränke trinken Sie am Tag? _____

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