Vitamin status after bariatric surgery: a randomized study of gastric bypass and duodenal switch1–3

Erlend T Aasheim, Sofia Björkman, Torgeir T Søvik, My Engström, Susanna E Hanvold, Tom Mala, Torsten Olbers, and Thomas Bøhmer

ABSTRACT

Background: Bariatric surgery is widely performed to induce weight loss.

Objective: The objective was to examine changes in vitamin status after 2 bariatric surgical techniques.

Design: A randomized controlled trial was conducted in 2 Scandinavian hospitals. The subjects were 60 superobese patients [body mass index (BMI; in kg/m²): 50–60]. The surgical interventions were either laparoscopic Roux-en-Y gastric bypass or laparoscopic biliopancreatic diversion with duodenal switch. All patients received multivitamins, iron, calcium, and vitamin D supplements. Gastric bypass patients also received a vitamin B-12 substitute. The patients were examined before surgery and 6 wk, 6 mo, and 1 y after surgery.

Results: Of 60 surgically treated patients, 59 completed the follow-up. After surgery, duodenal switch patients had lower mean vitamin A and 25-hydroxyvitamin D concentrations and a steeper decline in thiamine concentrations than did the gastric bypass patients. Other vitamins (riboflavin, vitamin B-6, vitamin C, and vitamin E adjusted for serum lipids) did not change differently in the surgical groups, and concentrations were either stable or increased. Furthermore, duodenal switch patients had lower hemoglobin and total cholesterol concentrations and a lower BMI (mean reduction: 41% compared with 30%) than did gastric bypass patients 1 y after surgery. Additional dietary supplement use was more frequent among duodenal switch patients (55%) than among gastric bypass patients (26%).

Conclusions: Compared with gastric bypass, duodenal switch may be associated with a greater risk of vitamin A and D deficiencies in the first year after surgery and of thiamine deficiency in the initial months after surgery. Patients who undergo these 2 surgical interventions may require different monitoring and supplementation regimens in the first year after surgery. This trial was registered at clinicaltrials.gov as NCT00327912. Am J Clin Nutr 2009;90:15–22.

INTRODUCTION

An estimated 220,000 people underwent bariatric surgical procedures in the United States in 2008 (1). This treatment is associated with a pronounced weight loss, an improvement in several obesity-related medical conditions (2, 3), an enhanced quality of life (4), and a reduction in long-term mortality (5, 6). The high volume of procedures and the introduction of a laparoscopic surgical approach have resulted in lower postoperative complication rates (7, 8). However, the limited food intake and malabsorption that often follow these operations may lead to severe nutritional deficiencies, including anemia (9), loss of bone mass (10), protein malnutrition (11, 12), peripheral neuropathies (13), visual impairment (14, 15), Wernicke encephalopathy (16), and fetal malformations (17, 18). Despite an increasing number of patients undergoing weight-loss operations, there are currently no standardized guidelines for postoperative nutritional management and monitoring; therefore, prospective studies addressing these issues are required (19–22).

Currently used bariatric surgical procedures include gastric bypass, adjustable gastric banding, and biliopancreatic diversion. These techniques have different effects in terms of weight loss, improvement in obesity-related conditions, and complication rates (2). However, because there are few prospective comparative studies, it is challenging to identify which weight-loss operation is best suited to the individual patient (23). Both gastric bypass and biliopancreatic diversion with duodenal switch are viable treatment options in superobese patients [body mass index (BMI; in kg/m²): 50–60]. Duodenal switch induced greater weight loss than gastric bypass in uncontrolled series (24, 25), but may also cause more nutritional deficiencies due to malabsorption. Thus, this report proposes to describe changes in vi-
tamin status in superobese patients who underwent gastric bypass or duodenal switch in an unblinded, prospective, randomized controlled trial.

SUBJECTS AND METHODS

This study was conducted in 2 Scandinavian public health care centers. The study protocol was approved by the Regional Ethics Committees for Medical Research in Eastern Norway and the Local Ethics Committee at Sahlgrenska University Hospital, Göteborg.

Enrollment and randomization

Patients were enrolled between February 2006 and August 2007, and a 1-y follow-up was completed by October 2008. Written informed consent was obtained from all participants, who were informed about the possible benefits, side effects, and risks associated with the surgical interventions as well as the purpose of the study.

Patients were eligible if they classified as superobese (BMI: 50–60), were aged 20–50 y, and had failed to achieve sustained weight loss by nonsurgical measures. Exclusion criteria were previous bariatric or major abdominal surgery, severe cardiopulmonary disease, malignancy, oral steroid treatment, drug abuse, and severe psychiatric illness. These requirements are in line with the recommended indications for bariatric surgery (21).

Patients were randomly assigned to surgical procedure within the strata of sex, age (<35 y or ≥35 y), BMI (<55 or ≥55), and study center. Randomization was computer-driven (LabView version 7.1; National Instruments, Austin, TX). The participants were informed of the assigned procedure 1 wk before surgery.

Surgical intervention

The surgical procedures were either laparoscopic long-limb gastric bypass or laparoscopic biliopancreatic diversion with duodenal switch. For gastric bypass, a 25-mL ventricular pouch was created. The intestinal limb lengths were as follows: alimentary limb, 150 cm; biliopancreatic limb, 50 cm; and common channel, variable length. For duodenal switch, the sleeve gastrectomy was performed along a nasogastric tube of 30–32 F. The intestinal limb lengths were as follows: alimentary limb, 200 cm; biliopancreatic limb, variable length; and common channel, 100 cm (Søvik TT, Taha O, Aasheim ET, et al, unpublished observations, 2008).

Nutritional intervention

Vitamin status was examined at the baseline visit (mean: 10 wk before surgery) and at 6 wk, 6 mo, and 1 y after surgery. Patients followed a very-low-calorie diet (1000 kcal) for 3 wk immediately before surgery to reduce their liver size (26). Starting 1 wk after surgery, all patients were prescribed daily supplements of multivitamins, 100 mg iron sulfate, 1000 mg calcium carbonate, and 10 µg vitamin D₃. Multivitamins were made available free of charge to encourage the use of the same brand. Gastric bypass patients also received a vitamin B-12 substitute. The supplements are further detailed in Appendix A. Ursodeoxycholic acid (500 mg/d) was provided until 6 mo after surgery to reduce the risk of gallstone formation (27), except to patients who had undergone cholecystectomy (one patient in each surgical group).

After surgery, we intervened on defined concentrations for each vitamin. Because there was limited evidence available for establishing cutoffs for such intervention, we based the cutoffs on clinical judgment and set the values between the lower reference interval limits (20, 28) and concentrations associated with symptomatic avitaminosis. The patients received relevant top-up supplementation if concentrations were below these cutoffs: thiamine, 55 nmol/L; vitamin B-6, 11 nmol/L; vitamin C, 11 µmol/L; vitamin A, 0.9 µmol/L; 25-hydroxyvitamin D, 37 nmol/L; and vitamin E, 2.2 µmol/mmol (adjusted for serum total cholesterol and triacylglycerols). Blood samples were then collected after 4 to 6 wk. If the vitamin concentration was within the reference interval, top-up supplementation was discontinued.

During each visit, the patients were asked which supplements they used and how many times per week they used these supplements. We categorized patients who used a supplement ≥5 d/wk as a user of that supplement.

Biochemical analysis

Blood was collected by venipuncture after an overnight fast. Samples clotted 30 min at room temperature, serum was separated by centrifugation (1700 × g, 10 min), and aliquots were stored at −20°C (−80°C for riboflavin and vitamin C). Samples prepared at Sahlgrenska University Hospital were kept on dry ice (−57°C) for up to 24 h during transportation. Vitamin assays were performed within 28 d of blood sampling (riboflavin, 90 d).

We used HPLC to assay thiamine (thiamin pyrophosphate in EDTA-blood) (29), riboflavin (flavin mononucleotide in EDTA-blood; Chromsystems, Munich, Germany), vitamin B-6 (pyridoxal-5’-phosphate in serum; Chromsystems), vitamin A (serum retinol; Bio-Rad Laboratories, Munich, Germany), and vitamin E (serum α-tocopherol; Bio-Rad Laboratories). We analyzed serum samples for vitamin C (ascorbic acid) using a micromethod (30), 25-hydroxyvitamin D [the sum of 25(OH)D₂ and 25(OH)D₃] and 1,25-hydroxyvitamin D by radioimmunoassay (DiaSorin, Stillwater, MN), intact parathyroid hormone (PTH) by chemiluminoimmunometric assay (Diagnostic Products Corporation, Los Angeles, CA), and ionized calcium with a Rapidlab 348 analyzer (Instru-Med Inc, Atlanta, GA). All vitamins, PTH, and calcium were assayed at Aker University Hospital. Other laboratory analyses were performed with Hitachi (717 or 800) Modular multianalyzers (Boehringer Mannheim, Mannheim, Germany) in the Departments of Clinical Chemistry at the 2 institutions. The vitamin interassay CVs ranged from 3% to 9%, except for 25-hydroxyvitamin D (14%) (20).

Thiamine was analyzed in heparin-blood in the Swedish participants. To adjust for potential effects of using this anticoagulant instead of EDTA, we measured thiamine concentrations in both heparin-blood and EDTA-blood in 30 patients and used the Passing-Bablok regression to determine this relation: EDTA value = (heparin value × 1.10) + 2.03. Reported thiamine concentrations correspond to EDTA values.

Statistical analysis

The main outcome measures reported were changes in vitamin A, thiamine, riboflavin, vitamin B-6, vitamin C, 25-hydroxyvitamin...
RESULTS

Participants

Patient flow throughout the study is shown in Figure 1. In total, 60 of 61 randomized patients underwent surgery. One patient decided to follow nonsurgical management and withdrew from the study, unaware as to which operation he had been assigned. All surgical patients completed each study visit (baseline, 6 wk, 6 mo, and 1 y), except for one patient at 1 y. Blood samples were not drawn from one patient at 6 mo or from one patient at 1 y. Thus, biochemical data were available from 237 of 240 study visits (99%). Baseline characteristics were not different between the surgical treatment groups (Table 1). Most patients were women (42 of 60) of Europoid ethnicity (57 of 60).

Water-soluble vitamins

Mean vitamin concentrations after gastric bypass and duodenal switch are shown in Figure 2. Thiamine concentrations changed in different ways in the 2 groups (P = 0.013 for time × procedure interaction): concentrations declined steeply and transiently after duodenal switch (P = 0.001 for change over time) but declined gradually after gastric bypass (P = 0.010).

Changes in riboflavin, vitamin B-6, and vitamin C were not different for the 2 surgical interventions (ie, no significant time × procedure interactions). Vitamin B-6 and vitamin C concentrations increased after surgery (P < 0.001 for both vitamins). Riboflavin concentrations did not change significantly after surgery. Vitamin B-12 concentrations were stable in duodenal switch patients and increased in gastric bypass patients, who used vitamin B-12 supplements. Data on vitamin B-12 and folic acid were only available in patients from one of the study centers (see Supplemental Table 1 under “Supplemental data” in the online issue).

Fat-soluble vitamins

We noted different changes in vitamin A and 25-hydroxyvitamin D concentrations in the 2 surgical groups (P = 0.002 and P < 0.001, respectively, for the time × procedure interactions).
Vitamin A concentrations declined after both gastric bypass \( (P = 0.003) \) and duodenal switch \( (P = 0.001) \), but the decline was greater in duodenal switch patients (Figure 2). Furthermore, 25-hydroxyvitamin D concentrations increased among gastric bypass patients \( (P = 0.001) \), but tended to decrease among duodenal switch patients \( (P = 0.059) \).

We found no significant time \( \times \) procedure interactions for PTH, ionized calcium, or 1,25-dihydroxyvitamin D \( [\text{data not shown for calcium and 1,25(OH)D}] \). PTH and ionized calcium concentrations did not change significantly after surgery. Serum 1,25-dihydroxyvitamin D concentrations increased during the 1-y follow-up \( (P < 0.001) \), data not shown).

There were no significant time \( \times \) procedure interactions for vitamin E or for vitamin E adjusted for serum lipids (total cholesterol + triacylglycerols). Unadjusted vitamin E concentrations decreased after surgery \( (P < 0.001, \text{data not shown}) \); however, adjusted vitamin E concentrations for lipids increased after surgery \( (P < 0.001) \) (Figure 2).

**Other markers of nutritional status**

Duodenal switch patients had a significantly greater mean (±SD) BMI loss than did gastric bypass patients from baseline to 1 y after surgery: 22.8 ± 4.7 compared with 16.3 ± 4.3 \( (P < 0.001, t \text{ test}) \). These values correspond to weight losses of 41% and 30%, respectively. We found time \( \times \) procedure interactions for hemoglobin \( (P = 0.008) \) and total cholesterol \( (P < 0.001) \), but not for triacylglycerols \( (P = 0.072) \). Duodenal switch
patients had lower mean hemoglobin and total cholesterol concentrations than did gastric bypass patients at each postoperative visit (Figure 3).

**Dietary supplements**

Duodenal switch and gastric bypass patients reported similar uses of the prescribed dietary supplements (Table 2). Multivitamins were used by 10% of patients at baseline and by 92% on average after surgery. Iron supplement use rates declined during the postoperative follow-up. Duodenal switch patients used additional supplements after surgery more often than did gastric bypass patients (16 of 29 compared with 8 of 31 patients; \( P = 0.020 \), chi-square test).

**Nutritional events**

One duodenal switch patient required parenteral nutrition for 2 wk because of severe hypoalbuminemia and lower limb edema 11 mo after surgery. Another duodenal switch patient required multiple intravenous iron infusions. Two patients had transient severe diarrhea (one in each surgical group). Three duodenal switch patients had protracted vomiting. These patients tended to have low thiamine concentrations 6 wk after surgery (454, 474, and 523 pmol/g hemoglobin). Two duodenal switch patients with very low vitamin A concentrations (0.7 and 0.8 \( \mu \text{mol/L} \)) underwent dark adaptometry (15), which showed night blindness, but none of them reported subjective recognition of visual impairment.

**Online supplemental material**

Data on mean corpuscular volume (MCV), folic acid, vitamin B-12, iron status, albumin, and the International Normalized Ratio (INR), which were obtained in patients from one of the study centers, are shown in Supplemental Table 1 under “Supplemental data” in the online issue. The proportions of patients with low concentrations of vitamins and hemoglobin are shown in Supplemental Table 2 under “Supplemental data” in the online issue. Duodenal switch patients more often had low vitamin A concentrations than did gastric bypass patients 1 y after surgery (13 of 27 compared with 2 of 31 patients; \( P = 0.001 \), Fisher’s exact test).

**DISCUSSION**

This report illustrates vitamin status changes in superobese patients who were randomly assigned to 2 different bariatric surgical procedures and were prescribed a standardized set of supplements after surgery. Compared with gastric bypass, duodenal switch was associated with lower postoperative concentrations of vitamin A and 25-hydroxyvitamin D and a steeper decline in thiamine concentrations. Additionally, duodenal switch patients had abnormal nutritional biomarker values more frequently than did the gastric bypass patients up until the first

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**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Gastric bypass (( n = 31 ))</th>
<th>Duodenal switch (( n = 29 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 6 wk 6 mo 1 y Baseline 6 wk 6 mo 1 y</td>
<td>Baseline 6 wk 6 mo 1 y Baseline 6 wk 6 mo 1 y</td>
</tr>
<tr>
<td>Multivitamin/mineral</td>
<td>13 90 90 87</td>
<td>7 97 100 89</td>
</tr>
<tr>
<td>Vitamin D/calcium</td>
<td>3 90 84 74</td>
<td>0 93 97 89</td>
</tr>
<tr>
<td>Iron</td>
<td>0 87 81 65</td>
<td>0 90 79 67</td>
</tr>
<tr>
<td>Added supplement(^1)</td>
<td>3 7 7 16</td>
<td>3 3 35 37</td>
</tr>
</tbody>
</table>

\(^{1}\)Use of each supplement was defined as taking that supplement for \( \geq 5 \) d/wk.

\(^{2}\)Added supplements at the 1-y follow-up included minerals and water-soluble vitamins (in both surgical groups) and fat-soluble vitamins (after duodenal switch).
year after surgery. This implies that duodenal switch patients may require different dietary supplements as well as different clinical and laboratory monitoring from gastric bypass patients during this period.

Vitamin status generally depends on diet, smoking, age, sex, season, and other factors. At baseline, many of the superobese patients had low concentrations of vitamin B-6, vitamin C, 25-hydroxyvitamin D, and lipid-adjusted vitamin E (see Supplemental Table 1 under “Supplemental data” in the online issue), as noted in other bariatric surgery candidates from the same region (20). Vitamin status after surgery is influenced by changes in eating patterns and nutrient intake, which may vary according to the surgical procedure (31). The postoperative anatomy influences nutrient absorption by altering biliary and pancreatic functions (32), intestinal transit speed, stomach production of hydrochloric acid, and bypassing primary intestinal uptake sites. Specific nutrient deficiencies may, in turn, decrease intestinal absorption or transport protein binding capacity for other nutrients. Biliopancreatic diversion with duodenal switch induces fat malabsorption due to a delayed mixing of food with pancreatic enzymes and bile acids (32). This could explain the lower concentrations of vitamins A and D observed after this procedure. After gastric bypass, inadequate secretion of intrinsic factor may lead to a vitamin B-12 deficiency (33). Vomiting and bacterial overgrowth in the small bowel may contribute to thiamine deficiency in bariatric surgery patients (16, 34). Obesity is associated with elevated concentrations of the inflammatory marker C-reactive protein (CRP) (35). Elevated CRP concentrations are associated with low serum concentrations of several vitamins, eg, vitamins B-6 and C (20, 36). A decline in CRP concentrations with weight loss (35) could be associated with higher vitamin concentrations after surgery. Use of vitamin supplements may also increase vitamin concentrations (37, 38).

Bariatric surgery may induce nutritional derangement. Within 6 mo after surgery, \( \approx 1 \) of 500 patients develops Wernicke encephalopathy because of severe thiamine deficiency (16). Vitamin B-12 deficiency is common after gastric bypass unless adequate supplementation is given (33). Pronounced folate deficiency is uncommon (39), but could have caused congenital neural tube defects in this group (18). Symptomatic deficiencies in riboflavin and in vitamins B-6, C, or E have rarely been reported in bariatric surgery patients (17, 40). We observed increased concentrations of these vitamins after surgery—a finding supported by others (37, 38). Malabsorptive weight-loss procedures may cause vitamin A deficiency, which in turn can lead to night blindness (15, 32). High rates of vitamin D deficiency have also been reported after malabsorptive bariatric surgery, as have frequent anemia and hyperalaminemia (41, 42). Duodenal switch was linked with a greater weight loss than gastric bypass, which confirms observations from retrospective series (24, 25). Thus, the nutritional effects observed in this prospective trial confirm findings from uncontrolled series using the same surgical procedures.

Our standard supplement regimen after surgery consisted of multivitamins, iron, calcium, and vitamin D supplements, and, additionally, vitamin B-12 for the gastric bypass patients. This treatment is similar to the regimen eventually used by most patients 2 y after gastric bypass, when patients started out on a single multivitamin preparation and were prescribed additional supplements if blood tests indicated inadequate nutrient status (22). Others have used higher dosages of vitamin A and vitamin D supplements after duodenal switch compared with the treatment used in this study (43). Our findings also suggest that the protocols for thiamine substitution need to be evaluated. Although 90% of our study patients used multivitamins after surgery, only 33% adhered to multivitamin use in one bariatric surgery series (39). Known predictors of poor adherence to medication include depression, treatment of asymptomatic disease, side effects, complexity, costs, and lack of belief in the benefit of treatment (44). These factors may be important for supplement adherence after bariatric surgery.

Comparisons of studies of vitamin status after bariatric surgery are challenging because of differences in study populations, surgical procedures, laboratory assessment, and dietary management. The strengths of our study include a prospective, randomized design; a high participant completion rate; assessment of vitamin status before surgery; and equal access to therapy because of universal health care systems in Scandinavia. The limitations of the study include vitamin status confounders, such as effects of preoperative management and changes in supplement use during follow-up. Although our study shows the effect of 2 bariatric procedures on vitamin status in a clinical setting, it does not address the relation between changes in vitamin concentrations and weight loss. The measurement of dietary supplement adherence via self-reporting is convenient, but has its shortcomings (44). The study had statistical power to compare weight-loss outcomes and was not designed to assess rare adverse events.

The findings from this study of superobese patients prescribed standardized dietary supplements suggest that, compared with gastric bypass, duodenal switch may be associated with greater risks of vitamin A and D deficiencies the first year after surgery and of thiamine deficiency for the initial postoperative months. After both procedures, riboflavin, vitamin B-6, vitamin C, and lipid-adjusted vitamin E concentrations remained stable or increased. Gastric bypass and duodenal switch may require different monitoring and supplementation regimes the first year after surgery.

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The authors’ responsibilities were as follows—ETA (guarantor), TTS, TM, TO, and TB: contributed to the study design and organized the study; ETA: analyzed the data and wrote the manuscript; ETA and TTS: cross-checked the data; ETA and TB: obtained funding; ETA, SB, TTS, ME, SEH, and TO: helped conduct the study; and TM, TO, and TB: supervised the study. All authors helped plan the study, interpret the data, and revise the manuscript. ETA, TTS, SEH, and TM have received travel grants and/or lecture fees from Johnson & Johnson and/or Covidien. None of the other authors reported any personal or financial conflicts of interest.

REFERENCES


APPENDIX A
Substitutive treatment after surgery

<table>
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<tr>
<th>Nutrient</th>
<th>Unit</th>
<th>Multivitamin(^1)</th>
<th>Other supplement(^2)</th>
<th>Recommended intake (women–men)(^3)</th>
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<td>Vitamin A (retinol)</td>
<td>μg</td>
<td>500</td>
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<tr>
<td>Vitamin D(^3) (cholecalciferol)</td>
<td>μg</td>
<td>5</td>
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<td>mg</td>
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<td>Folic acid</td>
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<td>1</td>
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\(^1\) Multivitamin/mineral pill (Nycoplus multi; Nycomed, Asker, Norway).

\(^2\) Iron sulfate (Fe\(^{2+}\)) 100 mg (Duroferon; AstraZeneca, Oslo, Norway), 500 + 500 mg calcium carbonate and 10 + 10 μg vitamin D\(^3\) (Calcigran forte or Kalcipos-D; Nycomed Pharma, Asker, Norway, and Recip, Solna, Sweden, respectively). Gastric bypass patients received cyanocobalamine [1 mg Betolvex (Actavis, Oslo, Norway) intramuscularly every 3 mo or 1 mg/d Behepan (Pfizer, Sollentuna, Sweden) oral supplement].

\(^3\) Data from Nordic Nutrition Recommendations (45).