

**Vitamin concentrations in Scandinavian obese subjects
undergoing surgical and non-surgical weight loss**

Erlend Tuset Aasheim



Faculty of Medicine

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Abbreviations

ANOVA	Analysis of variance
BMI	Body mass index (kg/m ²)
BPD	Biliopancreatic diversion
CRP	C-reactive protein
Duodenal switch (DS)	Biliopancreatic diversion with duodenal switch
Gastric bypass (GBP)	Long-limb Roux-en-Y gastric bypass
HOMA-IR	Homeostasis model assessment of insulin resistance
HPLC	High pressure liquid chromatography
NIH	National Institutes of Health
SOS study	Swedish obese subjects study
TPP	Thiamine pyrophosphate

Vitamins

Analytes

A	Retinol
B-1	Thiamine pyrophosphate
B-2	Flavin mononucleotide
B-6	Pyridoxine-5'-phosphate
B-9	Folate
B-12	Cobalamine
C	Ascorbic acid
25-OH-D	25-hydroxyvitamin D (the sum of D ₂ and D ₃)
E	α-tocopherol

1 List of papers

Paper I

Aasheim ET, Hofsø D, Hjelmesæth J, Birkeland KI, Bøhmer T.

Vitamin status in morbidly obese patients: a cross-sectional study.

Am J Clin Nutr 2008; 87: 362–9.

Paper II

Aasheim ET, Johnson LK, Hofsø D, Bøhmer T, Hjelmesæth J.

Vitamin status after gastric bypass and lifestyle intervention: a comparative prospective study.

*Manuscript ready for submission.**

Paper III

Søvik TT, Taha O, Aasheim ET, Engström M, Kristinsson J, Björkman S, Schou CF, Lönroth H, Mala T, Olbers T. Randomized clinical trial of laparoscopic gastric bypass versus laparoscopic duodenal switch for superobesity. *Br J Surg* 2009; accepted for publication.

Paper IV

Aasheim ET, Björkman S, Søvik TT, Engström M, Hanvold S, Mala T, Olbers T, Bøhmer T.

Vitamin status after bariatric surgery: a randomized study of gastric bypass and duodenal switch.

Am J Clin Nutr 2009; 90: 15–22.

* Paper II is based on data from a subgroup of the participants in a prospective trial. The manuscript is ready for submission, but is withheld pending submission of the main trial report.

2 Introduction

2.1 Obesity

Corpulence is not only a disease itself, but the harbinger of others

Hippocrates, 385 B.C. (1)

2.1.1 The burden of obesity

Is obesity a disease? This part of Hippocrates' alleged statement is still debated (2;3). However, few today would argue against the notion that obesity may lead to disease; in fact, the more severe obesity, the greater the risk of disease. The degree of obesity can be classified with the body mass index (BMI), a simple index of weight for height (4). BMI is defined as the weight divided by the square of the height (kg/m^2). It is the primary measure of obesity in this thesis, and most patients studied have BMI > 40. Furthermore, patients with BMI > 50 kg/m^2 are classified as "super-obese" (5).

Table 1. Classification of obesity according to World Health Organization (6).

Classification	BMI (kg/m^2)
Normal range	18.5 – 24.9
Overweight	≥ 25
Obese	≥ 30
Obese class I	30 – 34.9
Obese class II	35 – 39.9
Obese class III	≥ 40

A recent study examined the relationship between BMI and overall mortality in a collaborative analysis of data from nearly 900 000 adults (7). BMI was a strong predictor of overall mortality above the apparent optimum of about 22.5–25 kg/m^2 . At BMI 30–35 kg/m^2 , median survival was reduced by 2–4 years, and at

40–45, it was reduced by 8–10 years. The excess deaths were largely explained by cardiovascular disease, but also by other disorders (7). Other investigators have reported similar findings (8-13).

Studies have found positive associations between BMI and the risks of type 2 diabetes (14), cancers (15), asthma (16), urinary incontinence (17), and gastroesophageal reflux (18). Obese individuals are also prone to degenerative joint disease, gout, sleep apnea, nonalcoholic fatty liver disease, depression, and other conditions (19-21). Obesity during pregnancy is associated with both an increased health care expenditure (22) as well as an increased risk of transmission of obesity to the next generation (23). Obesity can reduce quality of life (24-26) and is associated with higher risks of disability and long-term sick leave (27-29). Thus, obesity does not only affect individuals but is a societal problem.

Some studies propose that waist circumference and/or waist-to-hip ratio are better than BMI at predicting the health risks associated with obesity (30-33). Abdominal obesity is more closely associated with excess storage of triacylglycerols in visceral fat depots than is BMI. This local energy “overflow” might increase disease risk in itself, or might alternatively be a marker of a systemwide impairment of energy storage (32). In morbidly obese and super-obese individuals, waist circumference is less useful in predicting health risk (34;35). Moreover, a limitation of all obesity classifications based on anthropometric measures is that they do not provide information on the extent of morbidity or functional limitations in a given individual (36).

2.1.2 Prevalence trends

Given obesity's detrimental effects and rising prevalence, it has become a major contributor to the global disease burden (21). The International Obesity Task Force estimates that there are more than 300 million people who are obese globally (1). International projections show that the number of obese people could quadruple within the next 20 years (37). By 2004, one third of the adult population in the United States population was obese, with 3% of men and 7% of women having a BMI > 40 (38). Telephone-based population surveys illustrate that it is the prevalence of severe obesity that has grown fastest in this country, where prevalence of BMI above 30, 40, and 50 increased by about 200%, 500%, and 900%, respectively, during 1987–2005 (39;40). Although lower than in the US, the prevalence of obesity has also increased in Norway (41;42). In 2002–2003, about 20% of Norwegian had a BMI > 30, with about 0.5–1% with a BMI > 40 (43). Preliminary data from health surveys conducted in 2006–2008 suggest a continued trend of increasing body weight in Norway (44).

2.1.3 Management

Obesity management includes lifestyle interventions (dietary advice, physical activity, and cognitive therapy), weight-loss drugs, and surgery. Dietary approaches can, in clinical intervention trials, confer an average weight loss of 2–6 kg after at least 1 year of follow-up (45-48). The degree of adherence to calorie reduction seems to be the primary effect of various dietary regimes. Although physical activity is particularly important in helping patients maintain a weight loss, it is considered less valuable for achieving the weight loss in itself (49). Behavioural and cognitive-behavioural strategies may help enhance weight reduction when combined with dietary and exercise strategies (50). Some individuals experience a larger weight loss in intensive treatment programs, but these are exceptions rather than the rule (51;52).

Anti-obesity drugs have shown modest effects on weight. A meta-analysis showed that long-term weight loss with orlistat, sibutramine, or rimonabant was only 3–5 kg greater than with placebo (53); direct comparisons of the drugs are lacking. Adverse effects differ between the drugs, and have led to withdrawal of rimonabant from the European market (53;54). As these drugs are expensive, and patients may have to pay out of pocket, cost can also prohibit continued use. In a retrospective cohort analysis, only 2% of patients persisted with orlistat or sibutramine therapy at 2 years (55). This may be a testament to the overall satisfaction with the drugs.

The management and prevention of obesity is, albeit seemingly easy in principle, a huge challenge within primary care settings (56). The modern world is ill-equipped to help individuals balance the intake and expenditure of calories as cars, elevators, desk jobs, televisions, and cheap, calorie-dense foods are in abundance. Weight loss is usually followed by weight re-gain. This may be explained by complex physiological systems, which cause compensatory increases in food intake and slowing of metabolism after weight loss (57;58). Reports from the United States have proposed that unless something is done to reduce the rising prevalence of people with BMI > 35, current life expectancies may decrease (59). All of the above provides a compelling rationale for taking a population-based approach to the prevention of obesity (20;40). It has also inspired the need for surgical treatment in those who have already become severely obese.

2.2 Surgery

This surgical treatment of obesity has achieved a respectable place in the armamentarium of a responsible and thoughtful surgeon (...) obesity clinics offering near ideal medical, psychiatric, dietetic, and social support achieve results that are no more than fair. Relapse is the rule, and there is a wide gap between effort expended and results achieved

Jack Farris, 1969 (60)

2.2.1 Relevance

The most commonly used criteria for obesity surgery were set by a National Institutes of Health (NIH) consensus conference in 1991, which stated that obesity surgery can be considered in patients with BMI > 40 kg/m² (or BMI > 35 in those with obesity-related comorbidities such as type 2 diabetes, sleep apnoea, or osteoarthritis) (61). Weight loss surgery, or bariatric surgery, has increased dramatically during the last decade (**Figure 1A**). This increase can be attributed to several reasons. Research has shown that more people are severely obese today than ever before; that severe obesity is associated with increased morbidity and mortality; that non-surgical treatment yields unsatisfactory weight loss; that surgery can yield favourable long-term effects on obesity-related conditions and mortality; that surgical safety has improved; and that surgical intervention appears to be cost-effective (62-65). Furthermore, the transition to laparoscopic techniques is linked with increased expenditure on surgical equipment, which motivates the involvement of the medical industry. In the United States, better coverage from insurance companies might also have contributed to an increased use of bariatric surgery (66).

The types of surgical techniques used have changed markedly. This can be illustrated by data from Sweden, where gastric bypass now dominates (**Figure 1B**). The next chapter reviews current techniques.

2.2.2 Surgical techniques

Surgical treatment of obesity is traditionally based on two mechanisms: restricting gastric volume and bypassing parts of the small intestine. These mechanisms can be used either in isolation or combined.

Various surgical techniques have been used over the past 50 years (67-69). Jejunioleal bypass was popular during the 1960s and 1970s, but was abandoned as many patients developed liver failure and other metabolic complications (70). Vertical banded gastroplasty was common during the 1980s and 1990s but has now been replaced by other techniques.

Figure 1A. Annual numbers of bariatric procedures in the United States.

Data are courtesy of American Society for Metabolic and Bariatric Surgery

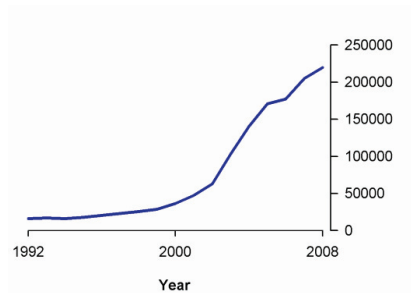
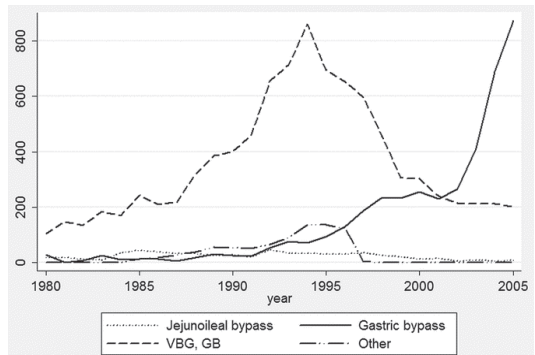


Figure 1B. Annual numbers of bariatric procedures in Sweden. VBG, vertical banded gastroplasty; GB, gastric banding; Other, other gastroplasties.

Reproduced from Marsk et al (71) with permission



Present bariatric procedures can be divided into 3 categories: purely restrictive (adjustable gastric band and sleeve gastrectomy); restrictive with some malabsorption (gastric bypass); and restrictive with substantial malabsorption (biliopancreatic diversion).

The adjustable gastric band is an inflatable silicone device, which is placed around the proximal portion of the stomach. This band can later be adjusted by instilling or removing saline via a subcutaneous access port. The intervention represents some 40% of bariatric procedures worldwide, but is rarely used in Norway (62;69). The sleeve gastrectomy consists of a partial, longitudinal, and pylorus-preserving gastrectomy. This technique is growing in popularity, albeit few data are available on long term outcomes.

Roux-en-Y gastric bypass accounts for about 50% of bariatric procedures worldwide and 90% in Norway (62;69). This technique was first described by Mason and Ito (72), where the upper part of the stomach is transected to create a very small gastric pouch of about 30 mL. This pouch is anastomosed to a Roux-en-Y proximal jejunal segment, bypassing the remaining stomach, duodenum and a small part of the jejunum. Although the length of the Roux (alimentary) limb can vary, it is often 150 cm (**Figure 2**) (73;74).

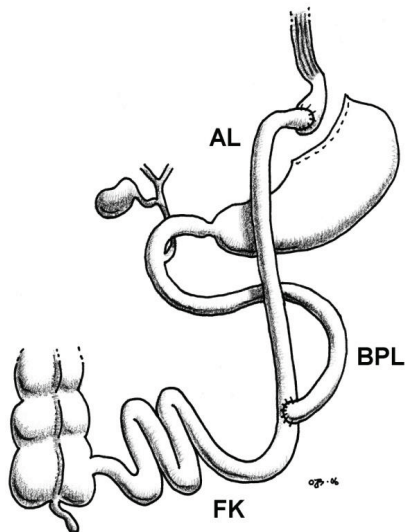
Biliopancreatic diversion type operations represent 5–10% of bariatric procedures in Europe and Norway (62;69). The operation was pioneered by Scopinaro (75), who uses a partial gastrectomy to create an

upper gastric remnant of 200–500 mL. The distal 250 cm segment of small intestine is isolated from the proximal segment. The proximal portion of this distal segment is anastomosed to the gastric remnant (alimentary limb), whereas the distal portion of the proximal segment (biliopancreatic limb) is anastomosed to the distal part of the ileum, 50–100 cm from the ileocecal valve. Digestion and absorption of nutrients are largely limited to this 50–100 cm “common channel”, where food mixes with bile and pancreatic enzymes. Biliopancreatic diversion was later modified by Hess and Hess, who instead performed a sleeve gastrectomy and a type of “duodenal switch” (Figure 2) (76). In heavier patients (BMI >60 kg/m²), a 2-step approach may be used. With this approach the patient first undergoes isolated sleeve gastrectomy, and the duodenal switch is completed after a phase of weight loss (77;78).

Figure 2. Surgical procedures, illustrated with specifications for papers III–IV.

Figures by Ole-Jacob Berge. Reproduced from Aasheim et al (62) with permission

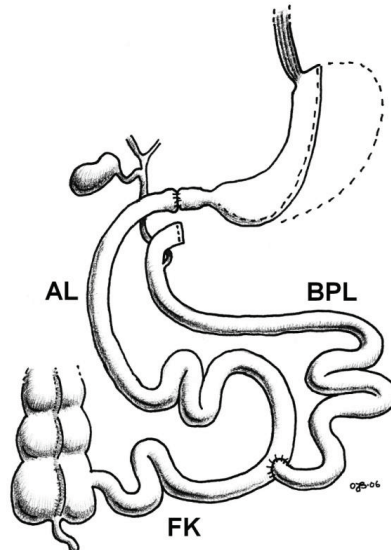
Long-limb Roux-en-Y gastric bypass



AL, alimentary limb; BPL, biliopancreatic limb; FK, common channel.

A gastric pouch of about 25 ml is created. The intestinal limb lengths are: 150 cm AL, 50 cm BPL, and variable length common channel (FK).

Biliopancreatic diversion with duodenal switch



A partial longitudinal gastrectomy is performed. The duodenum is transected 4 cm distal to the pylorus, and a “duodenal switch” is then performed. The intestinal limb lengths are: 200 cm AL, variable BPL, and 100 cm common channel (FK).

Most bariatric procedures are now performed by laparoscopy, which has radicalised bariatric surgery. As opposed to open surgery, a laparoscopic approach is associated with both a quicker recovery and fewer wound problems (79). However, the laparoscopic techniques are challenging and require trained surgical expertise (73;80).

Bariatric surgical techniques were originally designed to physically restrict food intake and induce energy malabsorption (81). However, it has now been proposed that additional effects may contribute to weight loss after surgery. This is especially the case with procedures that bypass segments of the small intestine. Putative mechanisms include changes in food preferences (towards less energy-dense foods) (82); changes in the meal-related secretion of appetite-modulating gut hormones (83); prolonged gastric emptying (84); and increased energy expenditure (85) after surgery. Further understanding of these mechanisms can potentially help design new interventions to facilitate weight loss.

2.2.3 Effects and complications

It is important to note that the current literature on the field of bariatric surgery lacks rigorous, randomised studies. For instance, of all studies included in a meta-analysis from 2009, less than 5% were randomised clinical trials, and less than 2% were high-quality randomised trials (19). Thus, due to a limited quality of evidence, one must be cautious in comparing the effects of such surgical procedures, especially with regards to safety (79). This also makes it challenging to identify which weight-loss operation is best suited to the individual patient (86;87). **Table 2** shows an overview of benefits and risks of present procedures.

Table 2. Relative benefits and risks of bariatric procedures (19;87-94)

	Gastric banding	Gastric bypass	Biliopancreatic diversion ± duodenal switch
Weight loss	+	++	+++
Comorbidity improvement	+	++	+++
Surgical safety	+++	++	+
Metabolic safety	+++	++	+

The SOS study

The Swedish Obese Subjects (SOS), although not a randomised trial, provides a good account on the effects of bariatric surgery. This prospective intervention trial compared 2010 morbidly obese patients wanting surgery with a matched control group of 2037 obese patients not wanting surgery. Some features of the study should be acknowledged. The SOS study began in 1987, before the criteria for bariatric surgery were proposed by NIH in 1991. Owing to different selection criteria for surgery, patients in the SOS study are older and have a lower BMI than most other bariatric surgery cohorts (19;88). Furthermore, treatment in the control group was not standardised. Of the operated patients, only 13% underwent gastric bypass, while 19% underwent gastric banding and 68% underwent vertical banded gastroplasty (88). Consequently, most patients were operated with a procedure that is now rarely used.

Weight and comorbidities

Weight loss often peaks 1 year after bariatric surgery. This is usually followed by a period of weight regain. In the SOS study, mean body weight loss 10 years after surgery was 25% for gastric bypass, 16% for vertical banded gastroplasty, and 14% for gastric banding. This was in contrast to patients in the control group, who had an average weight change of $\pm 2\%$ during the observation period (88).

Bariatric surgery reports often describe weight loss as “percentage excessive body weight lost” (where pre-surgical weight above a BMI of 25 is defined as excessive). Using this terminology in their meta-analysis, Buchwald et al. reported that patients with at least 2 years of follow-up had mean excessive weight loss of 49%, 63%, and 74% after gastric banding, gastric bypass, and biliopancreatic diversion, respectively (19). Surgical procedures associated with greater weight loss also had greater effects on type 2 diabetes. After at least 2 years of follow-up, type 2 diabetes resolved in as many as 58%, 71%, and 96% after gastric banding, gastric bypass, and biliopancreatic diversion (19). Sleep apnoea, dyslipidaemia, and a range of other obesity-related conditions have also been shown to improve after surgery. In addition, women may have better pregnancy outcomes, and a lowered risk of developing cancer, after bariatric surgery (19;89;92;95-99).

Mental health and psychosocial status, including social relations and employment opportunities, may also improve for most patients after bariatric surgery (100). In the SOS study, changes in health-related quality of life followed phases of weight alterations, with peak improvements in the surgical group during the first

year. A 10% weight loss appeared to be sufficient for benefits on the quality of life (101). Other studies, using duodenal switch, also show improvement in health-related quality of life after surgery (102;103).

Long-term mortality

Bariatric surgery may have favourable effects on long-term mortality (88;104-109). In the SOS study, after an average follow-up of 10.9 years, the surgically treated patients had an adjusted hazard ratio for death of 0.71 (95% confidence interval 0.54–0.92) compared with patients in the control group (88). As mentioned, most patients in the SOS study were operated with gastroplasty or gastric banding, and not with gastric bypass. Ted Adams et al., however, compared 7925 gastric bypass patients and 7925 matched controls in a retrospective cohort study. In the gastric bypass group, deaths from all causes were reduced by 40%; from diabetes by 92%; from coronary artery disease by 56%; and from cancer by 60% (104). An important point here is that, in order for bariatric surgery to prove beneficial, operative mortality needs to be kept low.

Complications

The complications of bariatric surgery can be roughly divided in two groups: surgical complications and metabolic or nutritional complications.

The perioperative (30-day) safety of modern bariatric surgery has been evaluated in a prospective, observational study of 4776 consecutive patients operated during 2005–2007 (94). Perioperative death rates were 0% and 0.2% after laparoscopic adjustable gastric banding and laparoscopic gastric bypass, respectively. Corresponding rates for major adverse events were 1.0% and 4.8%. Buchwald et al reported similar findings in their 2007 meta-analysis, with mortality rates of 0.1%, 0.2%, and 1.1%, after adjustable gastric banding, gastric bypass, and biliopancreatic diversion with or without duodenal switch (all laparoscopic) (90). The meta-analysis also showed that mortality rates have declined in the recent years. Moreover, studies with less than 50 patients often had more than twice the mortality rates found in larger cohorts (90).

Alongside the type of surgery performed, institutional procedure volume, and surgeon experience, various patient characteristics have also been related to the risk of fatal and nonfatal operative events. Surgical risk might increase in patients with high BMI, male gender, old age, and certain coexisting conditions (eg. diabetes or sleep apnoea). However, findings vary across studies (73;94;105;110-112). When death does occur as a result of surgery, pulmonary embolism and anastomotic leaks are common causes. Other

potentially severe operative complications include cardiac or respiratory failure, bleeding, and rhabdomyolysis (73;110;113).

Resurgery can become necessary, also after the perioperative period. Possible indications include cholelithiasis (increased risk of gallbladder disease with weight loss); and bowel obstruction, which can occur from strictures, adhesions, or internal hernias (114). Revision of the bariatric procedure is sometimes performed due to inadequate weight loss (115). Reversal of the procedure, or elongation of the common channel, is rare but may be needed in patients with protein malnutrition (116-118). Plastic surgery is often indicated, as the large weight loss may lead to problems with excessive skin (119-121).

Nutritional and metabolic complications of bariatric surgery can occur from a few weeks postoperatively. Anaemia is a common complication. Up to 30–50% of patients may develop low hemoglobin levels after gastric bypass or biliopancreatic diversion (116;118;122;123). Iron absorption and iron status indicators are reduced after gastric bypass, especially in premenopausal women (124;125). Parenteral iron therapy may sometimes be required (126). Calcium absorption can also be decreased after bariatric surgery (127). Protein malnutrition, although rare, can be a severe clinical complication (117;128-130). Trace element deficiencies have also been reported, most notably for copper (131-139) and zinc (130;140-152).

Other conditions observed post surgery include liver failure (153-158); postprandial hyperinsulinaemic hypoglycaemia (158-161); nephrolithiasis (162); vision impairment (163;164); neurological complications (131;133;165); central pontine myelolysis (166); and birth defects in infants after maternal bariatric surgery (167;168). Several of these rare complications can occur as a result of vitamin deficiency.

2.3 Vitamins

Even though surgery for obesity is well established we have not yet arrived at a point where we are aware of all the metabolic consequences (...) only meticulous postoperative observation will ensure that we recognize and treat these complications before irreversible damage has been done

Printen and Mason, 1977 (169)

2.3.1 Vitamins and disease

Vitamins are essential for the normal function and growth of cells. Deficiency in a vitamin can, therefore, lead to disease. Scurvy, pellagra, and beriberi are all well-known vitamin deficiency disorders in humans. In the presence of these disorders, the deficiency of a specific nutrient precedes the onset of characteristic symptoms. These symptoms may be reversed upon supplementation with the nutrient in question.

Present nutritional research devotes considerable effort to study epidemiologic relationships between nutritional factors (eg. blood biomarkers) and the development of chronic disease (eg. cardiovascular disease or cancer) (170-180). In this context, cause-and-effect is difficult to establish, given both the distance in time to the development of disease and the plethora of potential confounders. For several vitamins, data from hypothesis-generating epidemiologic studies and in-vitro experiments have suggested that supplementation with the vitamin might have the potential to prevent disease. Although subgroups may exist who benefit from single-nutrient supplementation (181), vitamin supplementation has come out with a negative result in a number of large, long-term, well-conducted clinical research trials. For example, supplementation with B-6, folic acid, and B-12 lowered homocysteine but did not reduce the number of cardiovascular events (182-185); and supplementation with antioxidant vitamins C, E, and β -carotene did not reduce the risk of type 2 diabetes, vascular disease, cancer, or other major outcomes (186-192). Vitamin D supplementation has yielded mixed results on soft end points (193-196).

In this context, the field of obesity surgery and vitamins can be regarded as somewhat refreshing, as the bariatric surgery literature deals primarily with prevention and treatment of acute disease. First, however, we will consider vitamin status in obese people that have not undergone weight loss surgery.

2.3.2 Is vitamin status different in obese people?

An individual's risk of being deficient in a given vitamin can be assessed by several approaches, which include obtaining a medical history and physical examination; using standardised dietary assessments; measuring physiological responses relating to vitamin function; and direct measurement of vitamin biomarker concentrations in different tissues. In this thesis, vitamin status refers to vitamin biomarker concentrations in serum or blood.

Confounding can be an important limitation for studies of vitamin status. Potential confounding variables may therefore need to be taken into account when relating vitamin concentrations to other variables, to avoid possible misinterpretation of the result. Potential confounders encompass age, sex, ethnicity, smoking habits, alcohol intake, socioeconomic status, physical activity, season of blood sampling, and, naturally, dietary intake and supplement use (197-201). Other factors specific to the persons under study include certain diseases and drugs, which can also influence on vitamin concentrations. For example, metformin can impair vitamin B-12 absorption (202;203).

Reports on vitamin status and obesity

The relationship between vitamin status and obesity has been explored in some cross-sectional studies. Examples of these studies are shown in Table 3. The designs range from large population-based studies to small, targeted studies of obese and morbidly obese individuals. Some studies compare vitamin concentrations in different BMI groups, while other studies simply report the percentage of patients with low vitamin concentrations (ie. below a cut-off level; this is often referred to as vitamin deficiency).

Vitamins B-1 and B-2 concentrations were not measured in the population-based studies listed in Table 3 (197;204-206). Obese persons had similar concentrations of these vitamins as healthy people (207;208), while in morbidly obese patients, low vitamin B-1 concentrations were found in 0–29% (209-211). Vitamin B-6 concentrations were not significantly related to obesity in the National Healthy and Nutrition Examination Survey (NHANES 2003–2004) (205) or in the studies of moderately obese persons (207;208). However, in one report (not listed in Table 3), low vitamin B-6 concentrations were found in 64% of 22 morbidly obese patients scheduled for gastric bypass surgery (212). With folate and vitamin B-12, there is no apparent link between obesity and vitamin status. Vitamin C concentrations, however, show an inverse relation with obesity (197;199;204;206;207;210). Vitamin A (serum retinol) concentrations were not related to obesity in a population-based study (204), while low concentrations were

sometimes observed in persons with more severe obesity (147;207;210). Low 25-hydroxyvitamin D concentrations appear to be common in severely obese individuals (213;214). Vitamin E (α -tocopherol) levels seem to be mostly normal; however, few studies reported lipid-adjusted vitamin E concentrations (215).

Vitamin concentrations have also been related to other measures of obesity than BMI. Plasma ascorbic acid levels were inversely related to waist-to-hip ratio (206); serum tocopherol levels were inversely related to abdominal adiposity in some, but not all studies (216;217); and serum 25-hydroxyvitamin D levels were inversely related to percentage body fat content (201).

Low vitamin concentrations have obviously not only been related to obesity itself, but also to medical conditions that are linked with obesity. The metabolic syndrome, for example, was associated with lower concentrations of vitamin C and lipid-adjusted vitamin E (and a lower intake of fruit and vegetables) in NHANES III (218). Moreover, higher baseline plasma vitamin C levels (and, to a lesser degree, fruit and vegetable intake) were associated with a decreased risk of incident diabetes during follow-up in a prospective cohort study (219). As mentioned, however, supplementation with vitamin C and other antioxidants did not confer a benefit on outcomes related to type 2 diabetes (187;189). Because plasma vitamin C concentration is sometimes used as a measure of intake of fruit and vegetables, it was proposed that vitamin C concentration should be thought of as a proxy of other protective factors contained in fruits and vegetables that could decrease the risk of type 2 diabetes (220).

In summary, several studies have implied that obesity might be associated with low micronutrient concentrations. However, few studies have specifically targeted populations with more severe obesity. If severely obese patients have low micronutrient concentrations, this could potentially increase these patients' risk of developing severe deficiencies after obesity surgery – that is, if obesity surgery can cause vitamin deficiencies.

Table 3. Selected cross-sectional studies of vitamin status and obesity

Reference	Subjects	Association between vitamin concentration and BMI									
		B1	B2	B6	B9	B12	C	A	D	E	E/ lipids
Population-based studies											
NHANES (204;205)	>3180 men	-	-	↔	↓	↔	↓	↔	↔	↔	-
	>2970 women	-	-	↔	↓	↔	↓	↔	↓	↓	-
SU.VI.MAX (197)	1307 men	-	-	-	-	-	↓	-	-	↔	-
	1821 women	-	-	-	-	-	↔	-	-	↔	-
EPIC–Norfolk (206)	8593 men	-	-	-	-	-	↓	-	-	-	-
	10475 women										
Obese persons											
Moor de Burgos 1992 (207)	102 obese 33 controls	↔	↔	↔	↔	-	↓	↓	-	↔	↓
Harnroongroj 2002 (208)	270 obese 175 controls	↔	↔	↔	-	-	↓	-	-	-	-
Morbidly obese patients											
Percentage of patients with inadequate vitamin status											
Ernst 2009 (209)	>89 patients	0	-	2	3	18	-	0	25	2	-
Coupaye 2009 (210)	49 patients	25	-	14	4	10	47	14	16	0	-
Flancbaum 2006 (211)	141 patients	29	-	-	-	0	-	-	68	-	-
Madan 2006 (142)	100 patients	-	-	-	6	13	-	11	40	-	-
Paper I	110 patients 58 controls	↑	↔	↓	↔	↔	↓	↓	↓	↔	↓

NHANES, Third National Health and Nutrition Examination Survey (B-6 data: NHANES 2003–2004);

SU.VI.MAX, SUplémentation en Vitamines et Minéraux AntioXydants;

EPIC, European Prospective Investigation of Cancer; lipids, total cholesterol + triacylglycerols.

–, not reported; ↔, ↓, ↑, unchanged, decreased, or increased vitamin concentrations with increasing BMI.

The studies were identified by a non-systematic literature search and were considered for inclusion if vitamin data were reported as concentrations (or deficiency rates) in association to BMI (or obesity categories). Studies were given priority if they reported data for other vitamins than folate, vitamin B-12, and vitamin D alone.

2.3.3 Can obesity surgery cause vitamin deficiencies?

Vitamin B-1

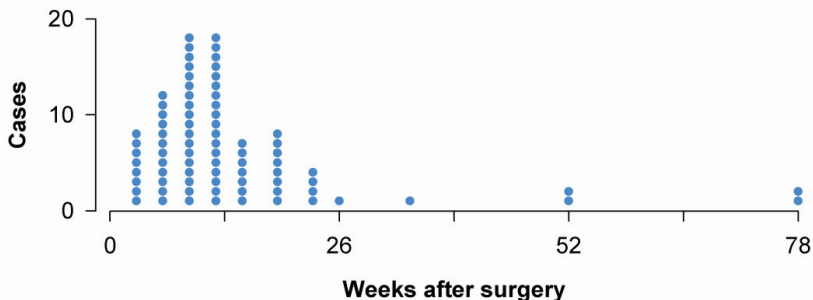
In August, 1975, a 23-year-old woman with a weight of 129 kg underwent an uncomplicated gastric bypass procedure to reduce weight. Here is an account of what followed:

Eight weeks postgastric bypass she had lost 27 kg and complained bitterly of vomiting seven to eight times per day. She was hospitalized, instructed in proper eating of small meals, and discharged within several days able to tolerate a liquid diet with difficulty. However, within one month she returned with persistent nausea and vomiting (...) Her weight at the time of discharge this time was 95 kg. She returned to the hospital in two weeks complaining of weakness, memory loss, inability to walk without help, and burning pain on the soles of both feet (...) She was placed on a regimen of thiamine 100 mg a day which dramatically improved her painful extremities as well as her memory loss (...) With continued thiamine intake the symptoms improved and the neuropathy disappeared (169).

This may be the first published account of Wernicke encephalopathy after gastric bypass, reported by Printen and Mason. Mason was also the surgeon who first described the gastric bypass operation (67). Since this report, numerous similar cases have been published and summarised (165;221).

Wernicke encephalopathy is caused by thiamine deficiency and the most common symptoms are ocular abnormalities, mental status changes, and incoordination of gait (222). When the condition presents after bariatric surgery, it is usually within the first postoperative months (**Figure 3**). Nearly all cases report

Figure 3. Time from obesity surgery to onset of Wernicke encephalopathy: dots represent individual patients. *Reproduced from Aasheim (165) with permission*



persistent, incessant vomiting before the onset of symptoms. The incidence of Wernicke encephalopathy after bariatric surgery was estimated to about 1 out of 500 patients after malabsorptive procedures, but the condition can also emerge after purely restrictive procedures (165). The first reported death from Wernicke encephalopathy after gastric bypass may have occurred at Aker Hospital, nearly 30 years ago (223). Appendix 1 shows an overview of reported cases.

Vitamins A and D

Vitamin A deficiency after bariatric surgery has led to night blindness, skin manifestations, and birth defects in children of mothers who had undergone weight-loss surgery. These complications occurred from only a few months to more than 10 years after surgery. Reported cases of vitamin A deficiency following presently used bariatric procedures are listed in the Appendix. In one series, night blindness was observed in 41 out of 1555 patients (2.6%) with more than 2 years of follow-up after biliopancreatic diversion (116). This was presumably without actively looking for the condition. Vitamin D deficiency years after bariatric surgery has, in severe cases, been related to increased fracture rates and osteomalacia. Identified reported cases are listed in the Appendix.

Vitamins B-3, B-6, folate, B-12, C, E, and K

Folate and B-12 deficiencies can cause megaloblastic anaemia, but also other, more severe complications. Folate deficiency has been linked with neural tube defects, and vitamin B-12 deficiencies with developmental delays, in the children of mothers who have undergone gastric bypass. Although rare, clinical deficiency in other vitamins have also been described after bariatric surgery. Pellagra-like dermatitis, sideroblastic anaemia, and scurvy were linked with deficiencies in vitamins B-3, B-6, and C, respectively, after gastric bypass. Severe vitamin E deficiency was believed to have caused ataxia several years after biliopancreatic diversion. Finally, vitamin K deficiency was associated with foetal bleeding following maternal weight-loss surgery. These cases are also listed in the Appendix.

It is evident that vitamin deficiency after bariatric surgery can cause severe clinical complications. While some of these complications are rare, they can have a dramatic influence on the patients' lives; and prevention is readily available. It is therefore important to know more about the changes in vitamin status in patients that undergo bariatric surgery.

2.3.4 Studies of vitamin status in obesity surgery patients

Many factors can interact to influence on a person's risk for vitamin deficiency after bariatric surgery. Dietary changes with restriction of food intake is one obvious explanation. The postoperative food preferences can vary according to the surgical procedure (224-227). Patients may also develop food intolerance. For instance, intolerance to meat is common after gastric bypass (228). Psychosocial factors can be important, as some patients develop food avoidance or anorexia after surgery (229-231).

The postoperative anatomy can impair nutrient absorption by several physiological mechanisms, which include changes in biliary and pancreatic functions; intestinal transit speed; stomach production of hydrochloric acid; removal of pyloric function; and bypass of primary intestinal uptake sites. Biliopancreatic diversion (with or without duodenal switch) induces fat malabsorption due to a delayed mixing of food with pancreatic enzymes and bile acids (116). This can have implications not only for the absorption of energy but also for uptake of fat-soluble vitamins (232). Diarrhoea is also more pronounced with the malabsorptive procedures. Vomiting and bacterial overgrowth in the small intestines have been proposed as mechanisms for thiamine deficiency after gastric bypass (233). Vitamin B-12 deficiency after gastric bypass can be the result of several mechanisms: inadequate secretion of intrinsic factor from parietal cells (234); proteolysis of intrinsic factor (before it can bind B-12) by pepsin and trypsin (235); and poor digestion of protein-bound vitamin B-12 due to achlorhydria and rapid intestinal transit (236).

Deficiency in one nutrient can also have implications for other nutrients. For instance, zinc deficiency can limit the ability to synthesise retinol binding protein, which can lead to a functional vitamin A deficiency (237). A pharmacologic study showed great interindividual variability in the effect of gastric bypass on atorvastatin bioavailability. The investigators speculated that this could be the result of individual differences in peristalsis and inflammation of the intestine early after surgery (238). Moreover, as the proximal small intestine has a high content of cytochrome P450 enzymes (which metabolise many drugs), bypass of this segment may lead to an *increased* bioavailability of drugs subject to intestinal first-pass metabolism (238). Similar mechanisms might potentially be relevant for the absorption and metabolism of micronutrients (239).

To summarise, bariatric surgical procedures impose changes in gastrointestinal physiology that can affect vitamin status. We have previously seen that some patients develop clinical vitamin deficiencies after surgery. But what changes can be found in vitamin biomarker concentrations after surgery?

Reports on vitamin status after bariatric surgery

An overview of selected studies of vitamin status after bariatric surgery is shown in Table 4. Vitamin B-1 has apparently not been measured in prospective studies of patients operated with gastric bypass or biliopancreatic diversion (with or without duodenal switch) (140). In retrospective case series, low thiamine concentrations were found in 0–49% after surgery (140;233;240;241). Vitamin B-2 concentrations were low in 14% of patients in one single study (241). Vitamin B-6 inadequacy has been reported in 10–18% (140;212;241). Folate and vitamin B-12 inadequacy rates vary widely. According to one report, 80% of patients developed inadequate B-12 concentrations during 2 years of follow-up (140). Low vitamin C concentrations were found in 35% in one study (241), while other investigators reported stable or increased vitamin C concentrations post surgery. Vitamin A concentrations were low in 10–17% of patients after gastric bypass and in 2–69% after biliopancreatic diversion with or without duodenal switch. Vitamin D inadequacy have been reported in up to 60% after gastric bypass and up to 76% after malabsorptive surgery. Vitamin E concentrations have been reported to decline after both gastric bypass and duodenal switch.

From these studies, it appears that the more malabsorptive procedures may be associated with a greater risk of developing inadequate vitamin levels. However, comparisons within and between the studies in the table are not straight-forward. Different supplements are often used in the various surgical groups.

What is the quality of the evidence?

It is important for clinicians to know which dietary supplements to recommend, how often to perform clinical check-ups, which blood biomarkers to measure, and when and how to intervene. The nutritional concerns for obesity surgery patients have been discussed in reviews (242-250) and management guidelines (87;251-253).

Medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient have been published as a joint effort from the American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery (251). Because of the paucity of high-quality scientific evidence, most recommendations were based on case series and expert opinions (251). In these studies, patient follow-up rate may be as low as 20–56% (123;142;144;241;254;255). Other limitations include a lack of standardisation of nutrient supplements; low adherence to supplements (255-257); or lack of reporting of adherence (123;141;142;254;258;259).

The reports often do not describe changes in supplement use during follow-up; laboratory methods; reference intervals; or inform about confounding variables. Few studies report data on vitamin status at baseline. All of these limitations, in union, make it difficult to interpret the findings from previous studies of vitamin status after bariatric surgery.

For most patients with severe obesity, bariatric surgery is the only treatment that is likely to lead to a major, sustained weight loss, alongside other proven benefits. Bariatric surgery is now performed on hundreds of thousands of patients each year. We know that this treatment can cause severe nutritional complications. However, knowledge on nutritional status in obesity surgery patients is, for the most part, based on uncontrolled studies. Yet these studies form the basis for how we care for modern-day patients. This has prompted our studies of vitamin status in obesity surgery patients.

Table 4. Selected studies of vitamin status after obesity surgery

	Patients (n), mean follow-up	Percentage of patients with inadequate vitamin status										
		B1	B2	B6	B9	B12	C	A	D	E	E/ lipids	
Gastric bypass												
Gasteyger 2008 (140)	137	2 y	4	–	13	45	80	–	–	60	–	–
Gong 2008 (141)	121	2 y	–	–	–	–	–	–	17	–	–	–
Lakhani 2008 (233)	80	NR	49	–	–	–	–	–	–	–	–	–
Avgerinos 2007 (260)	444	>2 y	–	–	–	–	–	–	–	↔	–	–
Atul 2006 (142)	100	1 y	–	–	–	8	0	–	17	19	–	–
Clements 2006 (241)	318	1 y	18	14	18	–	4	35	11	7	–	–
Johnson 2005 (261)	233	3 y	–	–	–	–	–	–	–	↔	–	–
El-Kadre 2004 (262) *	60	1 y	–	–	–	–	–	–	–	↓	–	–
Boylan 1988 (212)	22	1 y	–	–	10	10	5	–	–	–	0	–
Halverson 1986 (263)	74	3 y	–	–	–	38	64	–	10	–	–	–
Amaral 1984 (122)	144	2 y	–	–	–	18	40	–	–	–	–	–
Biliopancreatic diversion with or without duodenal switch												
Tonstad 2007 (240)	74	1 y	0	–	–	2	–	–	52	26	–	15
Marceau 2007 (264)	>500	7 y	–	–	–	0	1	–	2	15	–	–
Abbasi 2007 (258)	119	4 y	–	–	–	–	–	–	–	76	–	–
Dolan 2004 (144)	84	>2 y	–	–	–	–	–	–	60	50	5	–
Slater 2004 (149)	170	4 y	–	–	–	–	–	–	69	63	4	–

	Patients (n), mean follow-up	Percentage of patients with inadequate vitamin status										
		B1	B2	B6	B9	B12	C	A	D	E	E/ lipids	
Comparative studies												
Toh 2009 (254)	47 Ctr	1 y	-	-	-	0	0	-	-	38	-	-
	121 GBP	1 y	-	-	-	0	11	-	-	30	-	-
Coupaye 2009 (210) *	21 AGB	1 y	↓	-	↔	↔	↔	↔	↔	↔	↔	-
	49 GBP	1 y	↑	-	↔	↑	↓	↑	↔	↑	↓	↔
Granado-Lorencio 2008 (259)	72 GBP	1 y	-	-	-	-	-	-	↔	↔	↓	-
	115 BPD	1 y	-	-	-	-	-	-	↓	↓	↓	-
Ledoux 2006 (265)	110 Ctr	0 y	↔	-	↔	↔	↔	↔	↔	↔	↔	-
	51 AGB	1 y	↔	-	↔	↔	↔	↔	↔	↔	↔	-
	40 GBP	2 y	↔	-	↔	↑	↓	↔	↓	↔	↓	-
Paper II *	23 Ctr	1 y	17	-	9	4	0	13	0	10	0	0
	27 GBP	1 y	4	-	7	4	7	11	4	4	15	0
	23 Ctr	1 y	↔	-	↔	↔	↔	↔	↔	↔	↔	↔
	27 GBP	1 y	↔	-	↑	↑	↑	↔	↓	↔	↓	↑
Paper IV *	31 GBP	1 y	10	7	10	4	0	23	7	26	3	3
	29 DS	1 y	0	4	15	4	4	20	48	33	7	4
	31 GBP	1 y	↔	↔	↑	↔	↑	↑	↓	↑	↓	↑
	29 DS	1 y	↓	↔	↑	↔	↔	↑	↓	↔	↓	↑

AGB, adjustable gastric banding; BPD, biliopancreatic diversion; Ctr, control subjects; DS, duodenal switch; GBP, gastric bypass; lipids, total cholesterol + triacylglycerols.

-, not reported; *, prospective study; ↔, ↓, ↑, normal (stable), decreased, or increased vitamin concentrations.

The studies were identified by a non-systematic literature search and were considered for inclusion if the type of surgery was either gastric bypass or biliopancreatic diversion with or without duodenal switch. Studies were given priority if they reported data for other vitamins than folate and B-12 alone; were described as prospective; and if vitamin concentrations were compared with preoperative values or a control group.

3 Aims

The overall aim of this thesis was to study vitamin status in obesity surgery patients.

The specific aims were:

1. To compare concentrations of vitamins A, B-1, B-2, B-6, C, D, and E in morbidly obese patients with that in healthy controls.
2. To compare changes in concentrations of vitamins A, B-1, B-6, folate, B-12, C, D, and E after gastric bypass with the corresponding changes occurring after non-surgical weight loss.
3. To compare changes in weight in super-obese patients after gastric bypass and duodenal switch.
4. To compare changes in concentrations of vitamins A, B-1, B-2, B-6, C, D, and E after gastric bypass and duodenal switch.

4 Methods

4.1 Study designs

This thesis is based on three different studies: a cross-sectional study, where vitamin status in morbidly obese patients is compared with that in healthy controls; a prospective, non-randomised study, where changes in vitamin status after gastric bypass are compared with the corresponding changes after lifestyle intervention; and a prospective, randomised trial, which compares changes in vitamin status and weight after gastric bypass and duodenal switch.

Table 5. Numbers of study subjects in papers I–IV

Paper	Study design	Patient examinations					Controls
		Baseline	Intervention	6 weeks	6 months	1 year	
I	Cross-sectional	110	–				58
II	Non-randomised	50	23 Lifestyle			→	
			27 GBP			→	
III, IV	Randomised	60	31 GBP	→	→	→	
			29 DS	→	→	→	

Horizontal arrows (→) denote follow-up visits. GBP, gastric bypass; DS, duodenal switch.

The participants were recruited at Oslo University Hospital Aker in collaboration with Vestfold Hospital (papers I and II) and Sahlgrenska University Hospital (papers III and IV). Examinations were done during December 2005–November 2008. The intervention studies were not blinded.

4.2 Participants

All patients were referred from primary or secondary care for weight reduction treatment. In order to get a consultation at Aker, Vestfold or Sahlgrenska hospitals, patients needed to fulfill criteria that are commonly used as requirements for weight loss surgery (266): a BMI > 40, or BMI > 35 in patients with obesity-related conditions that infer a high cardiovascular risk (e.g. sleep apnea or diabetes mellitus) or induce physical problems interfering with lifestyle (joint disorders or body size problems interfering with employment, family function, or ambulation).

4.2.1 Cross-sectional study (paper I)

132 morbidly obese patients were recruited for this cross-sectional study between December 2005–April 2006. All were first-time visitors to the obesity outpatient clinics. Patients were excluded if they used multivitamin supplements ($n = 10$), refused to comply with study procedures ($n = 2$); were over 60 years of age ($n = 5$); were under current treatment for a severe psychiatric disorder ($n = 2$); had an alcohol intake > 50 g/day ($n = 2$); or had thyroid abnormalities ($n = 1$, excessive thyroxine substitution). The final study sample consisted of 110 patients. Mean BMI for this group was 45 kg/m².

58 non-obese controls were examined between January–May 2007 at the Hormone Laboratory, Oslo University Hospital Aker. Individuals recruited had responded to local advertisement at the hospital. Most of the controls were bioengineers or nurses. None had any chronic disease and none used medication or multivitamin supplements regularly. Persons using contraceptives ($n = 10$) or thyroxine substitution ($n = 4$) were included. Mean BMI for this group was 24 kg/m².

4.2.2 Non-randomised study (paper II)

Of the candidates for the cross-sectional study (paper I), 64 patients were examined at Vestfold Hospital. These patients were also considered for inclusion in a clinical trial, which compared the effects of bariatric surgery and intensive lifestyle intervention on obesity-related conditions. Among the 64 patients screened for enrollment into the trial, 53 were successfully included and underwent gastric bypass or lifestyle intervention. These 53 patients were included into the study of vitamin status after these treatments.

Allocation to treatment was made as a joint decision between patient and physician. The surgical group and lifestyle group had mean baseline BMIs of 42 and 47 kg/m², respectively. In addition to the

examinations at baseline, vitamin status was assessed 1 year after start of intervention. Of 53 included patients, 50 completed the follow-up.

4.2.3 Randomised study (papers III and IV)

60 Patients were recruited to the intervention study between February 2006–August 2007. In order to be eligible, patients needed to classify as super-obese (BMI 50–60 kg/m²), be aged 20–50 years, and to have failed to achieve sustained weight loss by non-surgical measures. Exclusion criteria were previous bariatric or major abdominal surgery, severe cardiopulmonary disease, malignancy, oral steroid treatment, drug abuse, or severe psychiatric illness.

The enrolled patients were randomly assigned to surgical procedure within strata of sex, age (< 35 y, or ≥ 35 y), BMI (< 55, or ≥ 55 kg/m²), and study centre. Vitamin status was examined before surgery; and 6 weeks, 6 months and 1 year after surgery. Mean BMI was 55 kg/m² at baseline in both surgical groups. Out of 60 operated patients, 59 completed the follow-up.

4.2.4 Clinical characteristics

Demographic data, medical history, and the use of tobacco, alcohol, drugs and vitamin supplements were recorded for all of the participants (papers I–IV). Anthropometry and blood pressure were measured with the use of standardised methods. Weight-related comorbidities (eg. sleep apnoea) were recorded based on the patients' medical history, as well as the information given by the physicians who referred the patients to bariatric surgery. Diabetes was diagnosed in patients with a history of diabetes (paper III) and/or fasting plasma glucose ≥ 7.0 mmol/L (papers I, II, and IV).

In paper I, Homeostasis Assessment Model insulin resistance was calculated in participants without diabetes from fasting concentrations of glucose and insulin using the calculator from the Diabetes Trials Unit (<http://www.dtu.ox.ac.uk>).

In paper II, dietary intake was assessed by structured 1-hour interviews performed by a registered dietician. Data on the patients' food intake during the preceding year were recorded on an optically readable food frequency questionnaire. The questionnaire, which encompassed 180 food items and beverages, was developed at the Department of Nutrition, University of Oslo. Previous versions of this questionnaire have been validated and used in national surveys (267;268). Portion sizes were either

defined in the questionnaire, or were estimated using of household measurement models. The interviews lasted for 1 hour on average. Questionnaire data were scanned using Teleform 10.0 (Cambridge, UK), and the dietary intakes were calculated using a database based on official food composition tables (Norwegian Nutrition Council, 1995). Calculations were done using a computer software called Kostberegningssystem (version 6.0), developed at University of Oslo.

4.3 Biochemical analysis

4.3.1 Blood sampling

Blood was collected by venipuncture after an overnight fast. For the vitamin assays, samples clotted 30 minutes at room temperature; serum was separated by centrifugation (1700 g, 10 min); and aliquots were stored at -20°C (-80°C for vitamin B-2 and vitamin C). Samples prepared at Vestfold Hospital or Sahlgrenska University Hospital were kept on dry ice (-57°C) for up to 24 hours when being transported to Oslo University Hospital Aker. Vitamin assays were performed within 28 days of blood sampling, except for vitamin B-2 (within 90 days) and 25-hydroxyvitamin D (within 1 year for papers I and II).

4.3.2 Biochemical assays

Routine laboratory analyses were performed at the Departments of Clinical Chemistry at the institutions where patients were examined. At Aker University Hospital and Sahlgrenska University Hospital, Hitachi Modular multianalyzers were used (717 and 800, respectively; Boehringer Mannheim, Germany), and at Vestfold Hospital, a Vitros 950 Chemistry System (Ortho-Clinical Diagnostics, Rochester, NY) was used.

We measured intact parathyroid hormone by chemiluminoimmunoassay (Diagnostic Products Corporation, Los Angeles, CA), and ionised calcium with a Rapidlab 348 analyzer (Instru-Med Inc., Atlanta, GA), at the Hormone Laboratory, Oslo University Hospital Aker.

4.3.3 Vitamin assays

Vitamins B-1, B-2, B-6, C, A, and E were analysed at the Nutrition Laboratory and 25-hydroxyvitamin D (the sum of D_2 and D_3) was analysed at the Hormone Laboratory; both at Oslo University Hospital Aker. Folate and vitamin B-12 were analysed at the Departments of Clinical Chemistry at the respective institutions. **Table 6** shows an overview of the methods used.

Table 6. Vitamin assays. *HPLC, high pressure liquid chromatography; RIA, radioimmunoassay.*

Vitamin	Specimen	Analyte	Method	Manufacturer
A	Serum	Retinol	HPLC (269)	Bio-Rad Laboratories
B-1	Blood	Thiamine pyrophosphate	HPLC (270)	In-house method
B-2	Blood	Flavin mononucleotide	HPLC (271)	Chromsystems
B-6	Serum	Pyridoxal-5'-phosphate	HPLC	Chromsystems
B-9	Serum	Folate	Multianalyser*	Boehringer Mannheim*
B-12	Serum	Cobalamine	Multianalyser*	Boehringer Mannheim*
C	Serum	Ascorbic acid	Micromethod (272)	Noncommercial method
D	Serum	25-hydroxyvitamin D	RIA (273)	DiaSorin
E	Serum	α -tocopherol	HPLC (269)	Bio-Rad Laboratories

*In paper II, folate and B-12 were measured at Vestfold Hospital using ADVIA Centaur (Siemens Medical Solutions Diagnostics) and Architect i2000SR (Abbot Diagnostics).

The inter-assay coefficients of variation (CVs) with these methods ranged from 3–14%, based on the analysis of ≥ 12 replicate samples on two different days. Vitamin assays included quality controls with high and low concentrations supplied by the manufacturer as well as internal controls. For vitamin B-1 and vitamin C, external controls were unavailable and standards were prepared from dry substances (Sigma-Aldrich, St. Louis, MO). Ascorbic acid and 25-hydroxyvitamin D were analysed in duplicate. In paper I, analysis of 25-hydroxyvitamin D was performed on the same day for patients and controls.

The Nutrition Laboratory had previously assessed preparation of specimens for vitamin C analysis, with respect to measured ascorbic acid concentrations after varying storage conditions. The results were very reliable when serum aliquots were frozen at -80°C within two hours of blood sampling, and analysed within 2 weeks. Other researchers have found similar storage conditions to be satisfactory (274).

4.3.4 Reference intervals

Reference intervals for concentrations of vitamins B-1, B-2, B-6, C, A, and E were calculated separately for men and women, based on mean \pm 2 SD vitamin concentrations among the healthy controls (paper I). Reference intervals for vitamins with a log normal distribution were obtained by calculating mean \pm 2 SD of log transformed values and back-transforming the result. For 25-hydroxyvitamin D, we used the reference interval from a previously described population (273).

For folate and vitamin B-12, we calculated the reference intervals based on findings in the control group (paper I) or used the reference intervals from the Departments of Clinical Chemistry at the relevant institution (papers II and IV).

4.4 Interventions and follow-up

4.4.1 Non-randomised study (paper II)

Surgery group

The surgical patients followed a preoperative low-calorie diet (900 kcal) for 3 weeks. Gastric bypass was performed by laparoscopy creating a gastric pouch of \approx 25 ml. The alimentary limb was measured to median 120 cm (range 80–200) cm and the biliopancreatic limb to median 100 cm (80–170). Patients received postoperative supplementation with a multivitamin/mineral formulation, vitamin D-calcium tablets (10+10 μ g vitamin D₃ and 500+500 mg calcium carbonate), ferrous sulphate, and fish oil supplements. Vitamin B-12 (1 mg cyanocobalamin) was given intramuscularly every 3 months. The supplements are further detailed in the Appendix and in paper II.

Lifestyle group

The lifestyle programme comprised four stays (one 4-week stay and three one-week stays) at a rehabilitation centre specialised in caring for morbidly obese individuals (Eveklinikken, 4735 Evje, Norway). The programme emphasised a cognitive approach, with the aim of enhancing motivation for lifestyle change. Patients were encouraged to attain 5–10% weight loss during 1 year by modifying eating habits and physical activity level. They were also encouraged to follow the recommendations provided by the Norwegian National Nutrition Council, which are in line with internationally used recommendations (275). Both individual sessions and group sessions were part of the program. When at home, the patients

were contacted by phone every two weeks and were encouraged to visit their general practitioner every four weeks. Dietary supplements or weight loss drugs were not routinely prescribed to the lifestyle group. At end of follow-up, 1 patient used orlistat and 1 used rimonabant.

4.4.2 Randomised study (papers III and IV)

Surgical procedures

The surgical procedures were either laparoscopic long-limb Roux-en-Y gastric bypass or laparoscopic biliopancreatic diversion with duodenal switch. These procedures are illustrated with specifications of the intestinal limb lengths in the Introduction (paragraph 2.2.2 Surgical techniques).

Patients received an infusion of 500 mL dextran (as thrombosis prophylaxis) and a single dose of 1500 mg metronidazole with 400 mg doxycycline preoperatively. Postoperatively, subcutaneous low molecular heparin was administered (according to weight) until 10 days after discharge.

Nutritional intervention

Patients followed a low-calorie diet (1000 kcal) for 3 weeks immediately before surgery to reduce their liver size (276). They received a liquid diet from the first postoperative day, a semiliquid diet after 1 week, and gradually returned to normal food intake after 2 weeks. Starting 1 week after surgery, all patients were prescribed daily supplements of a multivitamin, iron sulphate, and vitamin D-calcium tablets (10+10 µg vitamin D₃ and 500+500 mg calcium carbonate). Gastric bypass patients also received a vitamin B-12 substitute. Multivitamins were made available free of charge to encourage the use of the same brand. Additional details about the supplements may be found in the Appendix and paper IV. Ursodeoxycolic acid (500 mg/day) was provided until 6 months after surgery to reduce the risk of gallstone formation (277), except to patients who had undergone cholecystectomy (1 in each surgical group).

After surgery, we intervened on defined concentrations for each vitamin. As 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;29) and concentrations associated with symptomatic avitaminosis according to scientific literature (278;279). Patients received relevant top-up supplementation if vitamin concentrations were below these cutoffs: B-1, 55 nmol/L; B-6, 11 nmol/L; C, 11 µmol/L; 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 weeks. 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 weeks they used these supplements. We categorised patients who used a supplement ≥ 5 days/week as users of that supplement.

4.5 Statistics

Proportions were presented as numbers (%) unless stated otherwise. A Fisher's exact test or chi-square test was used to compare proportions between groups. Continuous data were presented as mean \pm SD or median (25–75 percentiles). Log transformation was used to obtain a parametric distribution when appropriate for further analysis. An unpaired Student's *t* test or Mann-Whitney *U* test was used to compare continuous data between groups. For all analyses, a two-tailed $P < 0.05$ was considered significant. No adjustments were made for multiple testing.

In paper I, we calculated Spearman's rank correlation coefficients to explore relations between continuous variables. Multiple linear regression was used to determine the strength of the associations between vitamin B-6 (log $\mu\text{mol/L}$) and various clinical variables.

In paper II, multiple linear regression was used to compare changes in vitamin concentrations after gastric bypass and lifestyle intervention. Adjustment was made for potential confounders, including baseline BMI.

Sample size for the randomised study (papers III–IV) was estimated based on the primary endpoint of the study, namely the difference in BMI change after the two surgical interventions. We estimated that 60 patients would give $>90\%$ power (2 sided *t* test, significance level 0.05) to detect a difference between the groups. This was based on a review of superobese patients at Sahlgrenska, who had BMI losses of (mean \pm SD, kg/m^2) 18 ± 6.7 and 25 ± 5.0 three years after gastric bypass or duodenal switch, respectively.

In paper IV, we used 2-factor repeated measures ANOVA to assess the effects of time as well as the interaction between time and surgical procedure for the nutritional biomarker outcomes. When there was a significant interaction between time and surgical procedure, we estimated the effect of time within each surgical group. Means were compared unadjusted, without imputation of missing data. We also employed

the Passing-Bablok regression when adjusting for the potential effect of using different anticoagulants for thiamine assays (280) in the Norwegian and Swedish patients.

Software packages used to perform statistical analyses and create graphics were SPSS versions 14.0, 15.0, and 16.0 (SPSS Inc., Chicago, IL), SamplePower 2.0 (SPSS Inc.), and SigmaPlot 10.0 (Systat Software Inc., San Jose, CA).

4.6 Ethics

4.6.1 Approvals

All participants were made aware of the purpose of the studies, and gave a written consent to participate. For the prospective studies, patients were carefully explained the possible benefits, side-effects, and risks associated with the interventions. The study protocols were approved by The Regional Ethics Committees for Medical Research in South Eastern Norway and The Local Ethics Committee at Sahlgrenska University Hospital, Göteborg, as applicable. The data management protocols were approved by the Norwegian Social Science Data Services.

4.6.2 Publishing guidelines

The prospective intervention studies were registered in ClinicalTrials.gov (identifiers NCT00273104 and NCT00327912), which is a database of clinical trials that is accessible to the general public. When preparing the manuscripts, we used checklists recommended by the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement (<http://www.strobe-statement.org/>) and Consolidated Standards of Reporting Trials (CONSORT) Statement (<http://www.consort-statement.org/>). We also followed the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE) (<http://www.icmje.org/>).

4.6.3 Role of the funding source

The sponsors of this work had no role in designing the studies; in collecting, analysing or interpreting the data; or in writing the reports.

5 Results

5.1 Paper I

Vitamin status in morbidly obese patients: a cross-sectional study

In this paper we compared vitamin status in patients with morbid obesity with that in healthy controls. Overall, vitamin status in the obese patients was strikingly different from that in the control group, with significant differences observed in six of nine vitamins assayed. Compared with controls, the obese patients had significantly lower mean serum levels of vitamins A, B-6, C, 25-hydroxyvitamin D, and lipid-standardised vitamin E. Conversely, patients had higher mean blood levels of vitamin B-1 than controls. The observations were consistent in both women and men.

5.2 Paper II

Vitamin status after gastric bypass and lifestyle intervention: a comparative prospective study

This report illustrates that gastric bypass patients attained a significant increase in vitamin B-6, folate, vitamin B-12, and lipid-adjusted vitamin E concentrations, and decrease in vitamin A concentrations, compared with patients who lost weight from a camp-based lifestyle intervention programme. No significant differences between the groups were found for vitamin B-1, vitamin C, and 25-hydroxyvitamin D. The contrasts in vitamin status changes between groups may have been related to dietary supplementation, which was only prescribed to the surgically treated patients.

5.2 Paper III

Randomised clinical trial of laparoscopic gastric bypass versus laparoscopic duodenal switch for superobesity

This paper reports on weight loss and surgical morbidity in an open label, randomised, controlled trial, where 60 patients were randomised to undergo either gastric bypass or duodenal switch. Patients in the two surgical groups had similar characteristics at baseline. Compared with gastric bypass, duodenal switch was associated with significantly longer operating time and longer postoperative stay. Complications tended to occur more often after duodenal switch than gastric bypass, both during the first 30 days (7 vs. 4 patients) and during the subsequent follow-up up until 1 year post (9 vs. 4) surgery; this was not statistically significant. BMI loss from baseline to 1 year after surgery was greater after duodenal switch (from 55.2 to 32.5 kg/m²) than gastric bypass (from 54.8 to 38.5 kg/m²).

5.3 Paper IV

Vitamin status after bariatric surgery: a randomized study of gastric bypass and duodenal switch

This paper illustrates vitamin status changes in the same patients as in paper III, who were randomly assigned to receive either gastric bypass or duodenal switch. All patients received a standardised set of supplements after surgery. Compared to gastric bypass, duodenal switch was associated with lower levels of vitamin A and 25-hydroxyvitamin D, and a steeper decline in vitamin B-1 levels, after surgery. Additionally, duodenal switch patients used top-up supplements more often than gastric bypass patients up until the first year after surgery. Levels of vitamins B-2, B-6, C, lipid-standardised vitamin E and folate were either stable or increased after surgery, and did not change differently in the two surgical groups.

6 Discussion

6.1 General context of main findings

In these reports we have investigated vitamin concentrations in morbidly obese patients, from treatment referral and up until 1 year after weight-loss intervention. At treatment referral the obese patients had strikingly different vitamin status from that in healthy individuals, with significantly lower concentrations in both fat-soluble and water-soluble vitamins. Serial measurements during follow-up showed that patients taking a set of dietary supplements had stable or increased concentrations of most vitamins after gastric bypass, while duodenal switch surgery was associated with a significantly greater decline in several fat-soluble vitamins as well as thiamine.

The study of vitamin status in bariatric surgery patients has traditionally comprised anecdotal case reports and retrospective patient series. Our studies thus extend on existing knowledge by providing some of the first prospective data on vitamin biomarkers in patients undergoing modern anti-obesity procedures. Although previous epidemiological studies noted low vitamin concentrations in obese individuals, few had characterised a range of vitamins in morbidly obese patients. Despite uncontrolled case series indicated that duodenal switch is associated with greater risk of nutritional compromise and greater weight loss than gastric bypass, these clinical endpoints had not been compared in a randomised, controlled setting.

What are the implications of this work? Deciding on which dietary supplements to prescribe and which vitamins to measure in blood tests is challenging for clinicians who treat bariatric surgery patients. Although our studies do not provide final answers to these questions, the findings may still give an inkling of where emphasis should be placed; and where further study should be undertaken. This discussion will resume after a methodological review.

6.2 Selected methodological considerations

This review will focus on vitamin biomarkers, standardisation of bariatric surgery research, and statistics.

6.2.1 Reading vitamin status

Dietary intake assessment

Food intakes show extensive day-to-day variation, both within and between individuals (281;282). Obese individuals tend to under-report dietary intakes, in particular snack-type foods outside normal meals (283-285). Although food frequency questionnaires are a better measure for capturing infrequent consumptions than, let us say, 24-hour dietary recalls, both methods are subjective and prone to a range of errors (286). Dietary intake assessment must thus be read with caution, especially in the case of vitamins (281). Consequently, it is unsurprising that we found no significant correlations between intakes and biomarkers of vitamins for the patients in the non-randomised study (unreported data from paper II).

Functional tests and clinical signs

Functional tests can be used to detect inadequate vitamin status, eg. erythrocyte transketolase activity is a measure of thiamine status; but direct measurement of vitamin concentrations generally has higher specificity and sensitivity (287;288).

Physiological tests are another approach to examine vitamin status. Dark adaptometry may be used to test for vitamin A deficiency, as was done for selected patients (who had serum retinol $<0.8 \mu\text{mol/L}$) in the randomised trial (**Figure 4**). The test is non-specific, as zinc and protein deficiencies may also impair dark adaptation (237). Of note, each identified patient with night blindness after bariatric surgery in anecdotal reports (see Appendix) had undergone malabsorptive surgery. This corresponds with a greater decline in serum retinol concentrations after duodenal switch than gastric bypass (paper IV).

Clinical signs relating to vitamin deficiency may be difficult to discriminate from signs which have non-nutritional causes, and symptoms usually develop only after tissue stores have become severely depleted (289). More sensitive diagnostics are thus needed to enable early prevention of nutritional deficiency.

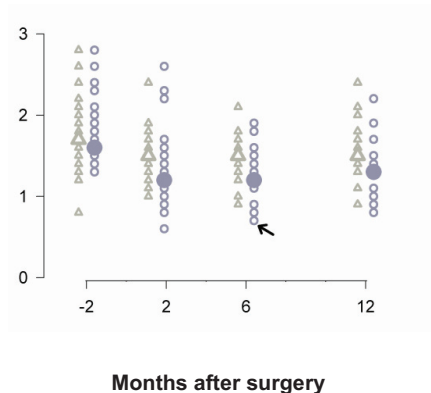
Vitamin biomarkers

As opposed to dietary intake and functional measures, vitamin biomarkers (205;287;290-297) offer the promise of being more convenient, specific, and sensitive tools for measuring vitamin status.

Figure 4. Example of correspondence between a vitamin biomarker (serum retinol) and a physiological test (dark adaptation).

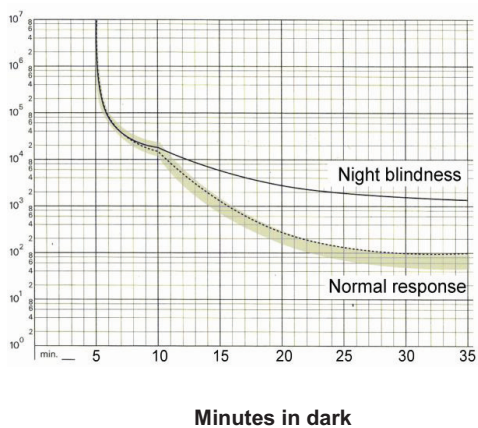
Serum retinol ($\mu\text{mol/L}$) after gastric bypass (Δ) and duodenal switch (\bullet). Large symbols represent medians and small symbols represent patients. The arrow indicates a patient with low serum retinol ($0.7 \mu\text{mol/L}$).

Data from paper IV (small symbols overlap)



The patient's sensitivity to light was tracked during dark adaptation (Goldman-Weekers); the test result indicated night blindness (solid line). After top-up vitamin A supplementation, serum retinol increased to $0.9 \mu\text{mol/L}$, and dark adaptation was normalised (dotted line). The shaded area represents normal responses.

Reproduced from Aasheim et al (298) with permission



Interpretation of the biomarkers nevertheless requires knowledge about the analyte and specimen examined. For instance, vitamin B-1 is present in blood as free thiamine, thiamine monophosphate, and thiamine diphosphate (TPP). TPP dominates quantitatively, has longest half-life, and acts as a coenzyme in decarboxylation reactions. TPP in blood exists mostly in cells, as TPP in plasma is dephosphorylated (299). Red cell TPP correlates strongly with whole blood TPP (287), and whole blood is the more convenient specimen (291). For these and other reasons, blood TPP is a preferred index for thiamine status (270;291). Adjustment of blood TPP for hemoglobin is often made (287;300), as in this work.

Reference intervals

Normal reference intervals for vitamin biomarkers are commonly defined as the range 95% of the population falls into. In contrast, the control group we used to generate reference intervals (paper I) was a convenience sample, and as such not likely to be representative of the general population.

In addition to reference intervals, it is important to know which concentration levels are associated with clinical avitaminosis. In the 1990s, our laboratory observed that 3 of 4 Wernicke encephalopathy patients had lower TPP concentrations than healthy controls (301). Clinical deficiency has also been associated with low concentrations of other vitamin biomarkers used in the thesis (278;279;301;302). Nevertheless, a limitation of the biomarkers is the imperfect ability to discriminate vitamin replete from deficient individuals. This relates to fluxes in dietary intake, homeostatic control mechanisms, and biological as well as analytical variability (303); which are discussed next.

Preanalytical errors

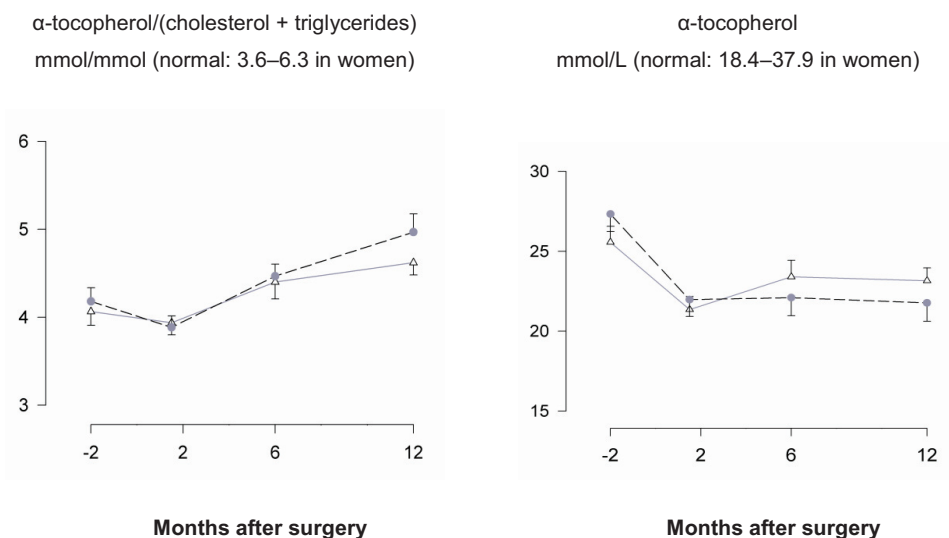
Most analytical errors are preanalytical errors (304;305); which can be controllable or uncontrollable (306).

Controllable preanalytical variables involve specimen collection and processing, which was performed according to established routine for this work (270;274;287). Although other researchers reported that the anticoagulant in test tubes did not affect TPP assay values (307), we found that TPP values were 10% higher when EDTA was used than heparin (280). We thus adjusted for the type of anticoagulant used during sample collection in paper IV.

Uncontrollable preanalytical variables relate to individual physiology (age, sex, underlying disease, etc). We aimed to limit diurnal and meal-related variations by collecting blood samples in the morning, after an overnight fast. Menstrual cycles may also influence on test results (308), but this is difficult to capture in morbidly obese women as they often have irregular menses. Seasonal variation was limited by examining patients and controls during the same months of the year (in paper I). Most subjects studied were of Europoid descent, which presumably limited variability related to race-ethnicity. In paper I, tobacco smoking was more frequent among patients than controls. This could have contributed to the lower vitamin C concentrations in the obese patients (199). Socio-economic status and physical activity level were not emphasised in the papers; rigorous data on these potential confounders were not collected.

Vitamin E illustrates preanalytical variation (**Figure 5**): α -tocopherol does not have a specific plasma carrier protein, but is transported non-specifically in lipoproteins. When considering the nutritional status of vitamin E, adjustment should thus be made for serum lipids (215). Surprisingly few reports on bariatric surgery have shown lipid-adjusted concentrations (210;240). Platelet tocopherol is an alternative vitamin E biomarker which does not depend on circulating lipid levels (309), but it is rarely used.

Figure 5. Example of a preanalytical variable: plasma lipids and α -tocopherol. Symbols denote mean (SEM) values after gastric bypass (Δ) and duodenal switch (\bullet). *Data from paper IV*



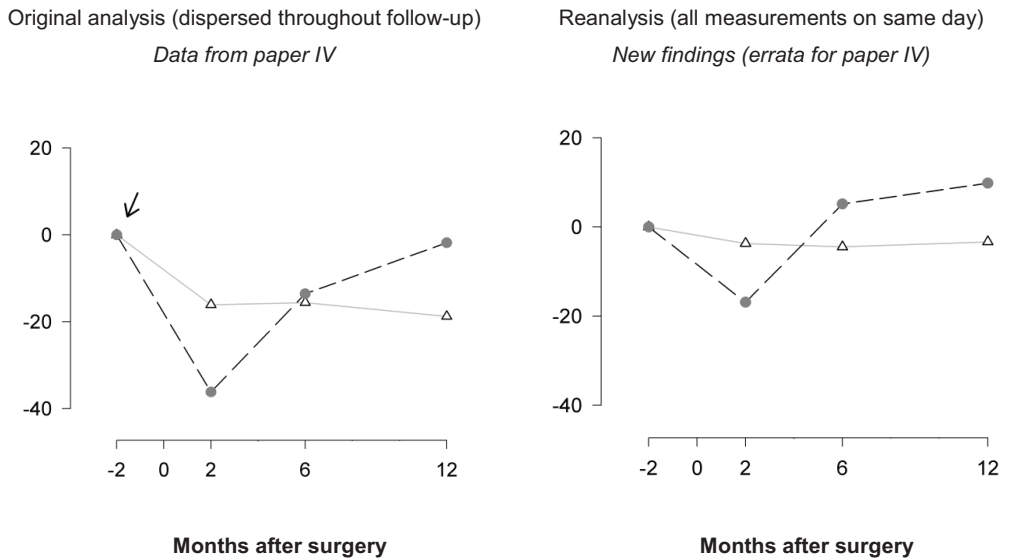
Analytical errors

Analytical errors involve technical-analytical problems in the laboratory. As all vitamin assays were performed in the same laboratory (except folate and B-12 in paper II), there was no inter-laboratory bias.

Between assay-variability is another potential problem. Paper IV illustrated thiamine status after gastric bypass and duodenal switch. Due to suspicion of analytical drift in the TPP measurements, we re-assayed TPP in patients from one of the study centres [who had frozen (-80°C) EDTA-blood specimens available], with use of a commercially available HPLC method (Chromsystems, Munich, Germany) (**Figure 6**).

Although the new findings confirmed that duodenal switch patients showed a steeper drop in thiamine concentrations early after surgery than gastric bypass patients, the drop was less pronounced than originally reported. Moreover, the original results suggested that patients had an overall decrease in thiamine concentrations from baseline to 1 year after surgery (median 11% decrease); while the new results indicated an increase after surgery (median 6% increase). The likely explanation for these discrepancies is that disproportionately high TPP values were obtained during the initial stages of the trial. Overall we concluded that gastric bypass patients had stable median thiamine concentrations during follow-up; whilst duodenal switch patients had a steeper drop early after surgery.

Figure 6. Example of analytical variation: median percentage change in thiamine (TPP/ Hb) after gastric bypass (Δ) and duodenal switch (\bullet). The arrow indicates values that are likely disproportionately high.



For the same reasons, assay variations might also have contributed to the finding of higher thiamine concentrations in obese patients than in healthy controls. As no stored blood specimens were available to test this hypothesis, the thiamine findings in paper I should be read with caution. Regrettably the quality control monitoring systems in our laboratory did not allow for a time trend analysis, and external quality assurance schemes are not always available for vitamin assays, as was the case for thiamine (287;310).

Postanalytical errors

A postanalytical error can occur when a correct test result is obtained, but incorrectly recorded. Aiming to limit such errors, we cross-checked data in databases and used descriptive plots to identify outliers.

Interpretation

Low vitamin concentrations in obese individuals can have several causes, which may differ across vitamins (206;311;312). This chapter discusses 1) systemic inflammation as a potential mechanism for low vitamin levels in obese individuals; and 2) changes in vitamin D–calcium status observed post surgery, which exemplify the need to interpret multiple biomarkers simultaneously because of compound physiology.

Systemic inflammation is associated with low plasma concentrations of numerous vitamins (**Table 7**). This may result from decreased transport protein (albumin) levels, increased turnover of antioxidant vitamins, shifts in tissue distribution of vitamins, and other mechanisms. Vitamin concentrations in red blood cells or whole blood may, at least for some vitamins, express nutritional status more reliably than plasma for patients with systemic inflammation (300). Obesity is associated with elevated concentrations of C-reactive protein (CRP), a marker of inflammation (313-318). When comparing our findings in paper I with other literature (Table 7), one might speculate that (obesity-associated) inflammation contributes to lowering serum vitamin levels in obese individuals; yet a causal relation has not been shown.

Elevated CRP levels are also associated with increased risk of a multitude of conditions that are in turn, associated with obesity (319-322). Disentangling causation from association is a major challenge when it comes to the inter-relationships between obesity, inflammation, vitamins, and disease. The association between depression and vitamin B-6 levels, which we explored in paper I, represents such a challenge.

Table 7. Example of a biomarker confounder: systemic inflammation. The arrows indicate the changes in vitamin concentrations observed in individuals with elevated CRP levels.

Vitamin	Morbidly obese patients		Various subjects		
	<i>Data from paper I</i>		<i>Table adapted from Aasheim and Bøhmer (323)</i>		
	Plasma	Blood	Plasma	Erythrocytes	Reference
A	↓		↓		(324-326)
B-1		↔ (↑)	↓	↔	(300)
B-2		↔	↓	↔	(300)
B-6	↓		↓	↔	(300;326-330)
C	↓		↓		(331)
E	↔		↓ ↔		(325;326;332)

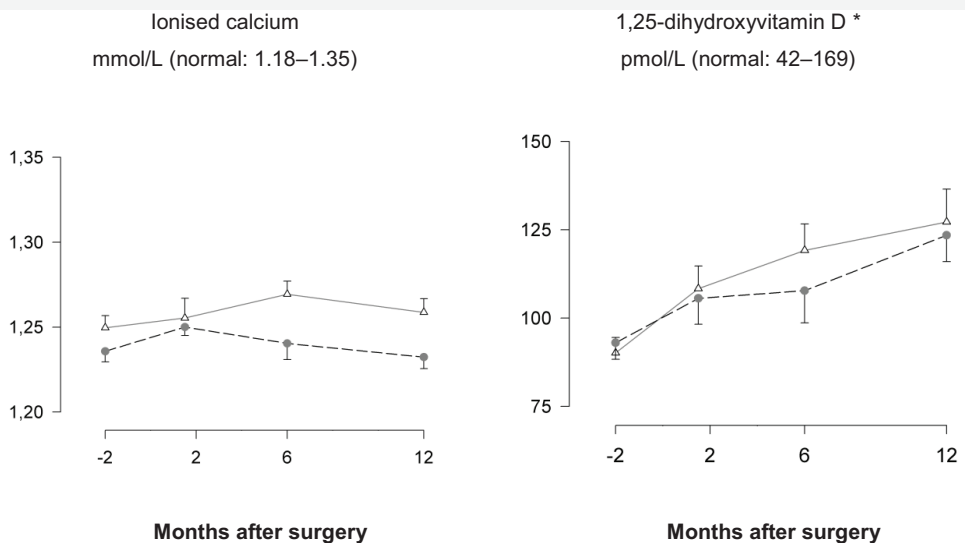
The studies were identified by a non-systematic literature search, and were considered for inclusion if blood vitamin biomarker concentrations were related to C-reactive protein levels.

Calcium homeostasis ensures regulation of calcium levels. Although calcium absorption may be impaired after gastric bypass and duodenal switch, the concentrations of calcium (**Figure 7**) as well as parathyroid hormone (paper IV) were mostly stable after both surgeries; possibly owing to supplementation.

Concentrations of 25-hydroxyvitamin D (ie. vitamin D stores) decreased after duodenal switch, but tended to increase early after gastric bypass. An increase in 25-hydroxyvitamin D after surgery could theoretically result from release of sequestered 25-hydroxyvitamin D from fat (311) during weight loss. Supplemental intake of vitamin D can likely also increase 25-hydroxyvitamin D levels. Although dietary vitamin D normally exists as D₂, the supplements prescribed contained D₃. Thus we could not have used a specific assay (discriminating D₂ from D₃) to assess the effect of supplementation on 25-hydroxyvitamin D levels.

Despite the varying changes in 25-hydroxyvitamin D, the concentrations of 1,25-dihydroxyvitamin D increased in similar ways after both surgeries (Figure 7). Other investigators have observed increased 1,25 dihydroxyvitamin D levels several years after surgery (258). Since 1,25-dihydroxyvitamin D acts to enhance calcium absorption, it is possible that a postoperative increase in 1,25-dihydroxyvitamin D levels is a physiological compensation for malabsorption of calcium .

Figure 7. Example of homeostatic compound physiology: calcium metabolism. Symbols denote mean (SEM) values after gastric bypss (Δ) and duodenal switch (\bullet). *Data from paper IV*



* Two-factor repeated-measures ANOVA: significant change after surgery ($P < 0.05$, time effect).

Multivitamins for everyone?

While patients with low vitamin levels and symptoms of deficiency may benefit from vitamin supplements, the implication of having a moderately low level with no associated symptoms is unclear. Should morbidly obese people, who appear prone to having low vitamin concentrations, use multivitamins “for insurance”?

The “triage allocation of micronutrients” hypothesis, which proposes to explain associations between low micronutrient levels and long-term disease development, states that scarce micronutrient availability activates mechanisms favouring short-term survival at expense of long-term health (eg. ATP synthesis favoured over DNA-repair) (333;334). Supporters of the hypothesis propose that the benefits and risks of micronutrient supplements can be assessed in short term studies, using surrogate outcomes (333). Another argument for using surrogate end points is the difficulty with obtaining definitive evidence from randomised controlled trials, due to the diseases studied (latency, many causes); the micronutrients (involved in several outcomes); the high costs (large populations needed, no commercial incentive); and low feasibility of such trials (poor long-term compliance, no “nutrient-free” control group) (333;335).

In 2006, however, a National Institutes of Health Conference Statement concluded that existing evidence is insufficient to recommend either for or against the use of multivitamin/mineral supplements to the general public to prevent chronic disease (336;337). In a subsequent study, elderly individuals supplemented with multivitamin/minerals had no benefits in cognitive function or morbidity from infections (338;339). For obese individuals, consequently, it might be more prudent to emphasise other nutritional advice, than to recommend use of dietary supplements.

6.2.2 Standardising methods

Surgical interventions may be more challenging to standardise than pharmacological interventions. This section addresses selected standardisation aspects which are relevant to our studies on bariatric surgery.

Surgery

Extensive training is required to master advanced laparoscopic surgery. One way to show an effect of learning is to review operating times, which drop significantly with experience and may eventually plateau after performing more than 100 gastric bypass procedures (73;80). Comparison of outcomes for different procedures may be prone to bias if a treatment centre has more experience with one of the procedures, as was the case in the randomised trial (papers III–IV).

Surgeons often individualise intestinal limb lengths, as was done in the non-randomised study (paper II). Although this is usually done to optimise weight loss, there is no consensus on the optimal limb lengths for different patient groups. In patients undergoing gastric bypass, some investigators have found increased weight loss with longer alimentary limb lengths (340;341), while others have not (342). The duodenal switch technique also differs in several aspects across treatment centres. The gastric pouch may be calibrated with bougies of varying diameter, and varying intestinal limb lengths are also created with this operation (78;149;343). The lack of standardisation complicates comparison across trials.

Although severe protein-calorie malnutrition appears to be more frequent in patients with a common channel length of 50–75 cm, patients with a 100 cm common channel may also develop malnutrition (117;118;240); this was observed in one patient after duodenal switch (papers III–IV). For some bariatric procedures there is thus a fine balance between adequate malabsorption and too much malabsorption, with no known way of predicting the result in a given patient. Super-obese patients may often want maximum weight loss. Indeed, who should define ideal weight loss for these patients, and by which criteria? Safety should be a primary concern in this provocative discussion.

Follow-up

The dietary supplementation regimens in papers II and IV were decided upon based on clinical experience, feasibility, and literature review; the regimens used were similar to those employed elsewhere (125;140;250;251;260;344;345). Although calcium citrate may have greater bioavailability than calcium carbonate after gastric bypass surgery (346), only calcium carbonate was available as a routine prescription drug in Norway and Sweden when the study was initiated. Absorption of vitamin B-12 appears to be more impaired after gastric bypass than biliopancreatic diversion (116;236), which is why we included B-12 supplements only for gastric bypass patients. Some investigators have advised higher dosages of vitamin A and vitamin D supplements after duodenal switch than used in our study (240;264).

We defined supplement use as intake of the supplement ≥ 5 times/week; a definition followed by others as well (257). Given that self-reporting has shortcomings (347), a biological marker to assess adherence might be useful. One suggested marker of non-adherence is a low serum folate level. Low serum folate is reported to be rare among bariatric surgery patients who take multivitamins (348), which is in agreement with our observations. Given that costs associated with supplement purchase may limit adherence (140), providing cost-free multivitamins (paper IV) may have enhanced multivitamin use. By setting the cut-off

levels for adding supplements below the lower reference interval limit (instead of at the lower limit), we aimed to observe the spontaneous changes in vitamin biomarkers in a typical clinical setting.

Experience may help reduce not only surgical, but also nutritional complications. In Scopinaro's series, 3 of the first 791 biliopancreatic diversion patients developed Wernicke encephalopathy; but after starting administration of thiamine to patients reporting small food intake early after surgery, none of the next 1450 patients developed Wernicke encephalopathy (349). It is thus relevant to note that the centers conducting the randomised study had less experience not only with performing duodenal switch surgery, but also with postoperative follow-up of duodenal switch patients, as compared with the gastric bypass intervention. Given this unbalance, we might furthermore subconsciously have tweaked the follow-up protocol towards management of gastric bypass patients when designing the randomised trial.

Weight loss metrics

Reaching consensus on how to report weight loss after bariatric surgery has proved challenging (350-356). Weight loss may be reported in kg, kg/m², percentage, and variants of the "excess weight lost".

In papers III and IV, we reported mean weight and BMI for various study visits, percentage excess BMI lost (paper III) and percentage body weight lost (paper IV). Strikingly, the difference in BMI loss between the 2 surgical groups was not reported in either paper, despite being the primary end point of the study. The difference was 6.5 kg/m² (95% CI, 4.1 to 8.8), where duodenal switch patients lost more weight.

6.2.3 Revisiting statistics and designs

This chapter comments on the statistical methods and study design employed for this work.

Paper I

Performing multiple statistical comparisons, as was done in the cross-sectional study, increases the likelihood of obtaining false-positive results. Then again, most differences in vitamin concentrations between patients and controls were highly significant ($P < 0.001$), which indicates robust findings. The lack of adjustment for confounding variables in the patient and control groups was a limitation of the study.

Paper II

In this paper we used multivariate regression to determine between-group significance for the change in vitamin concentrations. The use of 5 independent variables is conventional with a sample of 50 subjects.

Regression models including baseline vitamin concentration as independent variable were also tested; the R^2 obtained in these models were similar to those in the reported models. This may be unsurprising, as the change in vitamin concentration (which can depend on baseline concentration) was already in the model (meaning that adjustment for baseline concentration was already included). The non-randomised design of this study can be seen as a major limitation, as this confers a risk of having imbalanced confounding factors in the intervention groups. Few participants may increase the influence of extreme values on the results; the use of non-parametric statistics may partially have offset this disadvantage.

Paper III

In the randomised study, a history of depression was more common among duodenal switch patients than gastric bypass patients at baseline. Although we cannot rule out that this had impacts on patient outcomes, the difference between groups was the result of randomisation and not biased selection. We observed no significant difference in surgical complication rates between the intervention groups. This may be the result of a type II error, meaning that we might have been able to identify a difference if the study included more patients. Meta-analyses suggest that duodenal switch surgery is associated with more complications than gastric bypass (90;91).

The trial was not blinded. This might potentially have influenced on the patients' motivation to lose weight, given that duodenal switch was expected to confer greater weight loss than gastric bypass surgery. The investigators further had the dual role of being responsible for both patient follow-up and data analysis. This may have affected patient outcomes, eg. as a consequence of inadvertent enforcement of expected results.

Paper IV

We used 2-factor repeated-measures ANOVA to assess the effects of time and surgical procedure for the biomarker outcomes. An alternative approach would have been to use mixed-effects models, which have the advantages of using all available data and accounting for correlation between repeated measurements in the same subject (357). Mixed-effects analysis also have the drawback of being more demanding to implement. As our data set was nearly complete, we decided that the benefits of mixed-effects models would probably not justify the added effort.

6.3 Implications

6.3.1 Clinical management

Recruiting patients from 3 treatment centres may have increased the external validity of our findings. Aspects of our studies to keep in mind when applying our findings elsewhere include characteristics of the study populations; the surgical and non-surgical managements; durations of follow-up; biomarkers used; and institutional experience with the interventions.

Morbidly obese patients apparently often have low vitamin concentrations at referral for weight-loss treatment. This does not necessarily mean that these patients would benefit from taking vitamin supplements to raise vitamin concentrations. Although multivitamin supplementation may not be harmful, there is no evidence from controlled studies showing that supplementation is favourable for the patients.

Our findings indicate that different management protocols are needed for patients operated with gastric bypass and duodenal switch. Whereas gastric bypass patients taking the specified set of dietary supplements had mostly stable or increased vitamin concentrations after surgery, duodenal switch patients apparently had increased risk of vitamin A, D, and B-1 deficiencies during post-operative year one. Where laboratory assessment is possible, it may thus be more relevant to screen for deficiency in these vitamins after duodenal switch. The actions required when a low vitamin concentration has been detected in a bariatric surgery patient will depend on the patient's clinical context; and may involve further investigations, review of supplementation regimen, and additional follow-up. As blood thiamine measurement may take days to complete and tests are often not available (211), the primary concern with patients suspected to have thiamine deficiency is to urgently provide parenteral thiamine (165).

Measurement of folate and vitamin B-12 is often relevant, depending on the patient, the surgical procedure and the supplements used. Our findings (as well as identified literature) do not suggest that patients require routine monitoring of vitamins B-2, B-6, C, and E for the purpose of preventing avitaminosis in the short term after gastric bypass or duodenal switch.

6.3.2 Topics for further study

Further study could be undertaken to explore mechanisms which may potentially explain the low serum vitamin concentrations observed in morbidly obese patients. Another question is, do low serum concentrations found in severely obese individuals and normal weight individuals have the same implications? Measuring vitamin concentrations in several tissues (eg. red blood cells, fatty tissue, and serum), perhaps in conjunction with performing functional measurements, would be relevant for understanding the implications of obesity-associated low vitamin concentrations.

Although we conclude that gastric bypass and duodenal switch patients may require different follow-up, no explicit suggestions have been made. Our study evaluated 1 specified regimen of supplementation and follow-up for patients operated with 2 surgical procedures. To optimise follow-up regimens it would be better to conduct a separate study and compare, let us say, 2 follow-up regimens for 1 surgical procedure. Ideally, studies should be performed in large cohorts and with long term follow-up. Besides for dietary supplements, dietary advice given after bariatric surgery might also need to be reviewed. Other aspects of management that may need procedure specific guidelines include how often to perform clinical check-ups, which blood tests to take, and when and how to intervene (252). Patient satisfaction and costs associated with different supplements after bariatric surgery are additional topics of interest for future research.

Several nutritional safety aspects of bariatric surgery require further study. These include the assessment of fracture risk late after bariatric surgery; optimal management for preventing deficiency in vitamins B-1, A, and D (and possibly vitamin K) after malabsorptive bariatric surgery; and to further define the risk of deficiency in minerals and trace elements. Improving the therapy of Wernicke encephalopathy has general medical interest, as there is insufficient evidence to guide clinicians in the dose, frequency, and route of thiamine administration when treating this condition (358). Furthermore, the incidence of night blindness after malabsorptive surgery is largely unknown, and there are no management guidelines for this complication.

Additional clinical outcomes planned for publication from the randomised trial include long term changes in weight and morbidity; biomarkers relating to metabolic syndrome and cardiovascular risk; diet and eating patterns; gastrointestinal symptoms; and health-related quality of life.

7 Conclusions

Compared with healthy individuals, morbidly obese patients seeking weight loss had low concentrations of several vitamins, including 25-hydroxyvitamin D, vitamin B-6, vitamin C, and lipid-adjusted vitamin E.

Gastric bypass patients taking a feasible set of dietary supplements had mostly stable or increased vitamin concentrations after surgery, as compared both with baseline values and corresponding changes in a non-surgical control group not taking supplements.

Compared with gastric bypass, duodenal switch surgery was associated with greater weight loss; and appeared to be associated with greater risk for vitamin A and D deficiencies during the first year after surgery, as well as for vitamin B-1 deficiency early after surgery. Patients who undergo gastric bypass and duodenal switch to reduce weight may require different monitoring and supplementation regimens during the first year post surgery.

8 Appendix

8.1 Case reports of vitamin deficiencies after obesity surgery

Wernicke encephalopathy after obesity surgery

Reference	Wernicke signs*	Outcome at latest follow-up (months)†
Gastric bypass		
Printen 1977 (169)	M	▲ Memory improved, neuropathy disappeared (NR‡)
Solomon 1986 (359;360)	O M	● Recovered (0)
	O M A	▲ Polyneuropathy (12)
Kramer 1987 (361)	O M	▲ Korsakoff syndrome, suicide in nursing home (16)§
Kushner 2000 (362)	M A	● Recovered (5)
Salas-Salvadó 2000 (363)	O A	● Recovered (NR)
	O M A	▲ Slight cognitive deficit (24)
Sousa 2001 (364)	O	Unknown (NR)
Akhtar 2002 (365)	O M A	● Improved (NR)
	O A	● Improved (NR)
	O	● Improved (NR)
Chaves 2002 (366)	O M A	● Recovered (6)
	M A	▲ Muscle atrophy (12)
	M A	● Recovered (2)
	M A	● Recovered (2)
Gould 2002 (367)	O M	● Improved (NR)
	O	● Improved (NR)

	O		● Improved (NR)
Nakamura 2003 (368)	O M A		▲ Second WE incident, sensory deficit (10)
Escalona 2004 (369)	O M A		● Recovered (2)
Towbin 2004 (370)	O		● Able to walk, neuropathic pain reduced (6)
	O	A	● Recovered (2)
Nautiyal 2004 (371)	O	A	● Recovered (0)
Loh 2004 (372)	O M		▲ Memory deficits, nystagmus (4)
Foster 2005 (373)	O M A		▲ Quadriparetic, unable to converse (0)
Fandiño 2005 (229)		M A	▲ Amnesia, confabulation, apathy (24)
Parsons 2005 (374)	O M A		● Recovered, repeat brain MRI nearly normal (1)
Kulkarni 2005 (375)	O	A	● Recovered (NR)
Tariq 2006 (376)	O M		▲ Gait ataxia (3)
Worden 2006 (377)	O M		▲ Leg neuropathy, in rehabilitation facility (0)
Jiang 2006 (378)	O M A		● Recovered (6)
Alves 2006 (379)	O M		▲ Unable to walk (NR)
	O M		● Gradual improvement, able to walk (NR)
Sanchez-Crespo 2006 (380)	O M A		▲ Cognitive impairment, nystagmus (0)
Sullivan 2006 (381)	O	A	▲ Nystagmus, mild ataxia (30)
	O		● No focal neurologic deficits (0)
	O M		● Recovered (0)
Longmuir 2007 (382)	O	A	● Complete recovery (0)
Juhasz-Pocsine 2007 (131)		M	▲ Weakness and sensory ataxia (2)
		M	▲ Weakness and sensory ataxia (12)
Rodríguez Velasco 2007 (383)	O M		● No symptoms at 6 months follow-up (36)
Morel 2008 (384)	O M A		● Regression of symptoms (NR)

Chouillard 2008 (385) O M ● Rapid amelioration of symptoms (NR)

Gastroplasty

Rothrock 1981 (386) O A ▲ Required cane for ambulation (6)

Gardner 1982 (387) O M A ● Recovered (NR)

Oczkowski 1985 (388) O A ▲ Nystagmus (3)

Abarbanel 1987 (359;360) O ▲ Nystagmus, broadbased walk (18)

Albina 1988 (389) O M A ▲ Nystagmus (6)

Muñoz-Farjas 1996 (390) O A ● Recovered (12)

Seehra 1996 (391) O M A ● Recovered (NR)

O M A ● Recovered (NR)

Christodoulakis 1997 (392) O A ● Recovered (24)

Cirignotta 2000 (393) O M A ▲ Limited memory and motor deficits (8)

Toth 2001 (394) O M A ▲ Mild dysmetria and nystagmus (10)

Unknown author 2002 (395) O M ● Improved (0)

Watson 2003 (396) O M A ● Recovered (0)

Vanderperren 2003 (397) O M A ▲ Korsakoff syndrome, poor lower limb mobility (2)

Houdent 2003 (398) O M ● Memory improved (2)

Gastric partitioning

Milius 1982 (399) O M A ▲ Impaired memory, gait disturbance (0)

Sassaris 1983 (400) M ▲ Impaired memory (NR)

O M ▲ Impaired memory, used a walker (7)

Fawcett 1984 (401) O M A ● Recovered (NR)

Villar 1984 (402) O M A ▲ Gait ataxia (NR)

	O	A	▲ Mild gait ataxia (NR)
Paulson 1985 (403)		M	▲ Incomplete recovery, in nursing home (18)
	O	M	▲ Dementia, in state hospital (12)
	O	M	▲ Incomplete recovery, confused (NR)
		M	▲ Wheelchair, sudden death (6)
		M	▲ Incomplete recovery (NR)
	O	M	▲ Foot drop (12)

Gastric plication

MacLean 1982 (404)	O	M	A	▲ Minimal residual encephalopathy (NR)
Haid 1982 (405)	O	M	A	▲ Died in septic shock (0)§
	O	M	A	▲ Mild ataxia and memory deficit (0)
Somer 1985 (406)	O	M		▲ Lower limb muscle atrophy (12)

Gastric banding

Wadström 1989 (407)		M	A	● Recovered (24)
Bozborá 2000 (408)	O	M	A	● Recovered (5)
Sola 2003 (409)	O		A	● Recovered (0)

Gastric reduction

Ogershok 2002 (410)	O	M	A	▲ Mild ataxia, memory impairment (NR)
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Intragastric balloon

Chaves 2002 (366)		M	A	● Recovered (1)
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Sleeve gastrectomy

Makarewicz 2007 (411) O M ● Recovered (12)

Biliopancreatic diversion

Primavera 1993 (412) O M A ● Recovered (NR)

O M A ▲ Partial recovery (NR)

O M A ▲ Partial recovery (NR)

Fernández Santiago 2000 (413) O M A ● Recovered (NR)

* O, oculomotor abnormalities; M, mental status changes; A, ataxia or gait incoordination.

† Clinical status was defined as complete (●) or incomplete (▲) recovery.

‡ NR, not reported.

§ Autopsy demonstrated brain lesions consistent with Wernicke's encephalopathy.

¶ Part of case series with 3 men and 2 women aged 21–30 years (366).

|| Based on supplemental information obtained from the investigators.

The reports were identified by a systematic literature search conducted in 2008 (165). Jejunioileal bypass cases were not included.

Additional reports (not shown in the table) were subsequently identified by non-systematic literature search (221):

Lindboe 1981 (223), Rahman 2008 (414), Bhardwaj 2008 (415), Grao Castellote 2008 (416), Walker 2009 (417), Sebastian 2009 (418), Velasco 2009 (419), Schroeder 2009 (420), Richard-Devantoy 2009 (421).

Vitamin A deficiency after obesity surgery

Reference	Presentation	Surgical procedure
Aasheim 2008 (298)	Night blindness	BPD-DS
López-Rodríguez 2008 (422)	Night blindness	BPD
Smets 2006 (168)	Microphtalmia (infant)	BPD
Chae 2006 (164)	Night blindness	Intestinal bypass
Lee 2005 (423)	Night blindness	BPD-DS
Spits 2004 (424)	Night blindness	BPD
Hatzifotis 2003 (425)	Night blindness	BPD
Huerta 2002 (167)	Night blindness (mother) Congenital retinal damage (infant)	BPD
Smets 1999 (426)	Night blindness, optic neuropathy	BPD
Anastasi 1995 (427)	Night blindness, outer eye signs	BPD
Quaranta 1994 (428)	Xerosis	BPD
Castagneto 1994 (429)	Night blindness	BPD
Desirello 1988 (430)	Ocular symptoms	Total BPD (8 cases)

Reports were identified by a non-systematic literature search. Jejunioleal bypass cases were not included. BPD, biliopancreatic diversion; DS, duodenal switch.

Vitamin D deficiency after obesity surgery

Reference	Presentation	Surgical procedure
Al-Shoha 2009 (431)	Osteomalacia	BPD, gastric bypass
Benhalima 2009 (432)	Brown tumor	BPD
De Prisco 2005 (433)	Osteomalacia	BPD, gastric bypass
Atreja 2003 (434)	Osteomalacia	BPD-DS
Goldner 2002 (435)	Osteomalacia	Gastric bypass

Reports were identified by a non-systematic literature search. Jejunioleal bypass cases were not included. BPD, biliopancreatic diversion; DS, duodenal switch.

Miscellaneous vitamin deficiencies after obesity surgery

Reference	Presentation	Surgical procedure
Vitamins B-3, B-6, and C		
Ashourian 2006 (436)	Pellagra-like dermatitis	Gastric bypass
Lopez 2000 (437)	Pellagra-like erythema	Gastroplasty
Almhanna 2006 (139)	Sideroblastic anaemia	Gastric bypass
Prayaga 2005 (438)	Scurvy	Gastric bypass
Folate and vitamin B-12		
Molitero 2008 (439)	Neural tube defects	Gastric bypass
Martin 1988 (440)	Neural tube defects	Gastric bypass
Moschos 1998 (163)	Optic atrophy	Gastroplasty
Wardinsky 1995 (441)	Developmental delay in breastfed infant after maternal surgery	Gastric bypass
Grange 1994 (442)	Failure to thrive in breastfed infant after maternal surgery	Gastric bypass
Crowley 1983 (443)	Megaloblastic anaemia	Gastric bypass
Vitamins E and K		
Huerta (167)	Ataxia	BPD
Eerdekins 2009 (444)	Foetal and neonatal bleeding after maternal bariatric surgery	BPD, gastric banding

Reports were identified by a non-systematic literature search. Jejunioleal bypass cases were not included. BPD, biliopancreatic diversion.

8.2 Substitutive treatments

Nutrient	Unit	Paper II ¹	Paper IV ¹	Recommended intake ²
Vitamin A (retinol)	µg	500+250	500	700–900 ³
Vitamin D ₃ (cholecalciferol)	µg	5+20+10	5+20	7.5
Vitamin E (α-tocopherol)	mg	10+10	10	8–10
Vitamin B-1 (thiamine)	mg	1.4	1.4	1.1–1.4
Vitamin B-2 (riboflavin)	mg	1.6	1.6	1.3–1.7
Vitamin B-3 (nicotinamid)	mg	18	18	15–19
Vitamin B-5 (pantotenic acid)	mg	6	6	Not specified
Vitamin B-6 (pyridoxine)	mg	2	2	1.2–1.6
Folic acid	µg	200	200	300
Vitamin B-12 (cobalamine)	mg	1 ¹	1 ¹	2
Vitamin C (ascorbic acid)	mg	60	60	75
Vitamin K	µg	100	nil	Not specified
Calcium	mg	1000	1000	800
Chromium	µg	50	50	Not specified
Copper	mg	2	2	0.9
Iodine	µg	150	150	150
Iron	mg	65–130 ³	14+100	9
Magnesium	mg	100	100	280–350
Manganese	mg	2.5	2.5	Not specified
Selenium	µg	50	50	40–50
Zinc	mg	15	15	7–9

¹ Gastric bypass patients also received cyanocobalamine injections. For brand names and other details, see papers II and IV. ² Nordic Nutrition Recommendations (275). ³ Values are shown for women–men.

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10 Errata

Paper I

Thiamine pyrophosphate (TPP) was assayed in EDTA-blood in the healthy individuals, as opposed to heparin-blood for obese individuals. After publishing paper I, we learned that higher TPP assay concentrations may be obtained in EDTA-blood than heparin-blood. This means that if EDTA-blood had also been used for the obese patients, then patients might have had higher TPP concentrations than reported. As a result, the reported difference between groups (higher concentrations among the patients) could have been diminished by using two different anticoagulants. The comparison between patients and the controls is also hampered by analytical variation, as outlined in 6.2.1 (under “analytical errors”). Given these limitations it is difficult to conclude about any differences in TPP concentrations between the patients and controls.

Further specification of laboratory diagnostics made at Hospital of Vestfold: triacylglycerols, ALT, albumin, ALP, creatinin, phosphate, and C-reactive protein were measured using Vitros 950 Chemistry System (Ortho-Clinical Diagnostics, Rochester, NY); hemoglobin using Cell-Dyn 4000 hematology analyzer (Abbott Diagnostics, Ireland), and parathyroid hormone using Elecsys 2010 (Roche Diagnostics GmbH).

In Table 1, the mean C-reactive protein (CRP) concentrations in obese patients and healthy individuals erroneously included the patients from Vestfold Hospital. These patients should have been excluded, as the laboratory in Vestfold had a lower detection limit for CRP of 7 mg/L. When including only the patients from Aker (16 men and 35 women), the respective CRP values in patients and controls were as follows: women, 16.4 ± 15.8 vs. 1.2 ± 1.5 mg/L; and men, 6.7 ± 3.8 vs. 1.3 ± 0.8 mg/L ($P < 0.001$ for both; compared by *t* tests with use of log transformed CRP values).

In the rightmost column of Table 3, the “<” should be removed from the *P* value for vitamin A.

Paper II

Inaccurate author lists were given for references 2 and 16. The following is accurate:

Goldner WS, O'Dorisio TM, Dillon JS, Mason EE. Severe Metabolic Bone Disease as a Long-Term Complication of Obesity Surgery. *Obes Surg* 2002; 12: 685-92.

Reinehr T, de Sousa G, Alexy U, Kersting M, Andler W. Vitamin D status and parathyroid hormone in obese children before and after weight loss. *Eur J Endocrinol* 2007; 157: 225-32.

Paper IV

Clarification of vitamin D supplement dosage: whereas the main text lists 10 µg, the appendix lists 20 µg (10 + 10 µg). The information in the appendix is accurate.

Thesis

Discussion (6.1): "suplemens" was corrected to "supplements".

References: journal volume and page numbers were added for references 37, 56 and 168.

11 Papers I–IV

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