Nutrition Research Reviews (2023), 36, 512–525 doi:10.1017/S0954422422000221

Development and complications of nutritional deficiencies after bariatric surgery

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Abstract

The clinical effectiveness of bariatric surgery has encouraged the use of bariatric procedures for the treatment of morbid obesity and its comorbidities, with sleeve gastrectomy and Roux-en-Y gastric bypass being the most common procedures. Notwithstanding its success, bariatric procedures are recognised to predispose the development of nutritional deficiencies. A framework is proposed that provides clarity regarding the immediate role of diet, the gastrointestinal tract and the medical state of the patient in the development of nutritional deficiencies after bariatric surgery, while highlighting different enabling resources that may contribute. Untreated, these nutritional deficiencies can progress in the short term into haematological, muscular and neurological complications and in the long term into skeletal complications. In this review, we explore the development of nutritional deficiencies after bariatric surgery through a newly developed conceptual framework. An in-depth understanding will enable the optimisation of the post-operative follow-up, including detecting clinical signs of complications, screening for laboratory abnormalities and treating nutritional deficiencies.

Key words: **Obesity: Bariatric surgery: Nutritional deficiencies: Complications**

(Received 27 May 2022; revised 10 October 2022; accepted 21 November 2022; accepted manuscript published online 25 November 2022)

The double burden of malnutrition

In the past decades, obesity has become an international public health issue. The prevalence continues to increase at an alarming rate, even though there is a growing awareness regarding the burden of obesity[1]. Despite the likelihood of apparent overconsumption of calories in people with obesity, a paradoxical challenge is the co-existence of overnutrition alongside undernutrition known as the 'double burden of malnutrition'. Within an individual, household or population, the double burden of malnutrition manifests through the simultaneous development of undernutrition (e.g. stunting, wasting or nutritional deficiencies) alongside overnutrition (e.g. overweight, obesity or other diet-related non-communicable diseases) across the life course[2]. In reality, the double burden of malnutrition is more complex than a simple co-existence. Both undernutrition and overnutrition can propagate long-term effects due to interconnected biological pathways that involve metabolic dysregulation, inflammation and gut microbiome imbalance. Moreover, life-course exposure can increase the risk of developing non-communicable diseases by imposing a high metabolic load on a depleted metabolic capacity[3]. In case of scarcity, micronutrients will be allocated to the functions needed for short-term survival rather than those required for long-term health, also known as the triage theory[4]. The former will contribute to the development of certain chronic non-communicable diseases that are already prevalent in individuals with obesity (e.g. type 2 diabetes, cardiovascular disease or cancer)[5]. Due to the severity of health implications, the United Nations have provided an umbrella of policies, programmes and plans within their decade of action on nutrition that aims to eliminate malnutrition in all forms by 2030[6]. While there has been some progress, the prevalence of obesity continues to grow and is outweighing the efforts taken to prevent a further rise[1,7]. As prevention fails, obesity treatment remains pivotal.

Obesity management

Due to the multifactorial nature of obesity, treatment is challenging. To achieve weight loss and improve obesity-related risk factors, guidelines recommend lifestyle changes, pharmacotherapy or bariatric surgery depending on the severity of overweight and associated health risks[8,9]. Lifestyle changes should be the foundation of every obesity treatment. These changes include dietary

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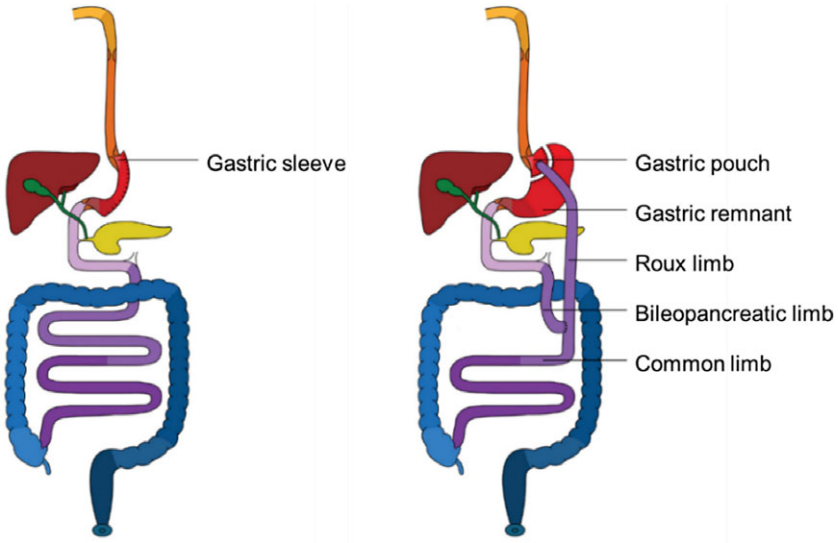

Fig. 1. Sleeve gastrectomy (left) and Roux-en-Y gastric bypass (right).

alterations, increased physical activity and behavioural training[8,10,11]. Failure of lifestyle change to induce (<5% of total body weight loss) or sustain (<1 year) weight loss indicates the necessity of complementary treatment options[8,10,11]. Pharmacotherapy can result in durable weight loss beyond what lifestyle changes alone may produce[8,10,11]. Until recently, long-term pharmacotherapy with suitable efficacy, tolerability and safety was perceived as a utopia. Nonetheless, recent studies showed that semaglutide at a dose of 2·4 mg can lower and sustain body weight loss by 15% after 1 year of treatment in combination with a diet and increased physical activity[12–14]. Although that amount of weight loss is clinically relevant, it may seem insignificant compared with the results obtained by surgical intervention. A range of surgical or bariatric procedures has been developed that historically has been categorised as 'restrictive', 'malabsorptive' or 'combined restrictive–malabsorptive'. Surgical procedures were deemed 'restrictive' when they limit food intake by reducing gastric volume, while procedures that affect nutrient absorption through an intestinal bypass were deemed 'malabsorptive'[15]. Although this approach sounded appealing at first, a vast amount of evidence supports that the underlying mechanism is profoundly physiological rather than solely anatomical[16,17]. Decades of research have now linked weight loss to reduced appetitive behaviour and potentially increased energy expenditure. Underlying mechanisms that associate the rearrangement of the gastrointestinal tract with the favourable metabolic outcomes include at least central appetite control, the release of gut hormones, changes in microbiota composition and diversity, and changes in bile acid levels. For now, the exact response, combination and timing of signals remain largely unknown[18]. To date, the main bariatric procedures are sleeve gastrectomy and Roux-en-Y gastric bypass. In a sleeve gastrectomy, the greater curvature of the stomach is longitudinally resected. In a Roux-en-Y gastric bypass, the stomach is reduced in size by forming a small gastric pouch without a pylorus and then a part of the small intestine is bypassed (Fig. 1)[19–21].

These anatomical changes trigger a vast amount of physiological and hormonal changes that contribute to the favourable aspects of bariatric surgery. Irrespective of the type of procedure, the beneficial outcomes include substantial weight loss, improvement of obesity-related comorbidities and prolonged survival[22–25]. Despite its effectiveness, bariatric surgery can result in complications due to the invasive nature of the procedure and the need for lifelong adjustment afterwards. Complications are commonly categorised into early (e.g. anastomotic leakage, gastrointestinal haemorrhage, internal hernia, obstruction, perforation, venous thromboembolism and wound infection) and late complications (e.g. anastomotic stricture, cholelithiasis, dumping syndrome, gastroesophageal reflux, gastrointestinal fistula, gastrointestinal ulceration, internal hernia, malnutrition, nutritional deficiencies and obstruction)[26–28]. Despite a diversity of complications, nutritional deficiencies are the most common repercussion of bariatric surgery.

Development of nutritional deficiencies after bariatric surgery

The pathological onset of nutritional deficiencies is not yet fully understood, but a variety of determinants are involved. Therefore, we developed a new framework to provide conceptual clarity on the role of key determinants in the development of nutritional deficiencies after bariatric surgery (Fig. 2). The framework acknowledges the immediate role of diet, the gastrointestinal tract and the medical state of the patient while highlighting different enabling resources.

Immediate and underlying determinants: diet

Vitamins and minerals are micronutrients that are essential for normal functioning, disease prevention and wellbeing. With some exceptions, micronutrients cannot be produced in the body and thus must be derived from the diet. If micronutrient intake is unable to compensate for its loss, nutritional deficiencies can arise with or without clinical symptoms and signs[29]. After bariatric surgery, a patient's diet can be inadequate to meet his/her nutritional needs due to different underlying

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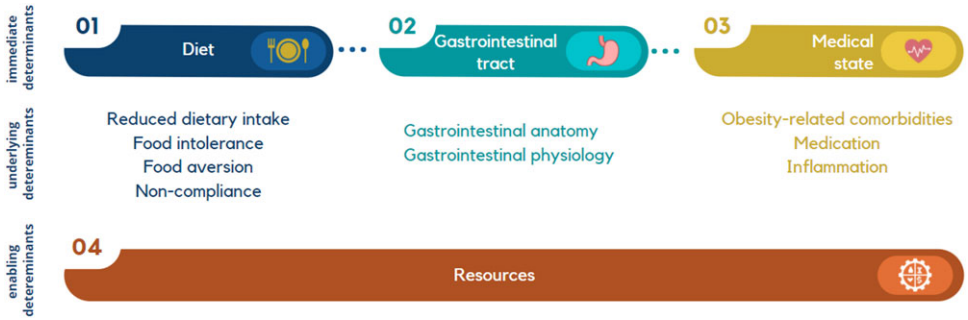

Fig. 2. Determinants of nutritional deficiencies after bariatric surgery.

determinants: (i) reduced dietary intake, (ii) food intolerance, (iii) food aversion and (iv) non-compliance with dietary and supplementation recommendations (Fig. 2).

Reduced dietary intake. To determine if there are changes in dietary intake, several studies investigated the impact of different bariatric procedures on overall energy intake. A recent meta-analysis observed that caloric intake decreased significantly after sleeve gastrectomy (weighted mean difference: 939·8 kilocalories (kcal)/d; 95% CI 647·66–1231·10) and Roux-en-Y gastric bypass (weighted mean difference: 1215·16 kcal/d; 95% CI 887·66–1542·67)[30]. The reduction in caloric intake goes hand in hand with a reduction in micronutrient intake. Inadequate intake of various micronutrients has been extensively investigated by different research groups after both sleeve gastrectomy and Roux-en-Y gastric bypass (Table 1)[31–45]. Importantly, different research methods and recommendations have been applied throughout these studies, although they do indicate inadequate micronutrient intake as a challenge after bariatric surgery[46]. While there is still some uncertainty regarding the dietary mechanisms underpinning this reduction in micronutrient intake, decreased portion sizes and altered food preferences are recognised as important players[47]. Evidently, the size of the gastric pouch or sleeve acts as a physical barrier for (excessive) eating initially after surgery[48]. Therefore, specific eating behaviours are recommended, including but not limited to eating at a slow pace (specific dietary recommendations are reviewed elsewhere)[49]. In addition, post-operative changes in appetite, smell and taste may drive changes in food preference[50]. Food cravings may be exacerbated in cases of nutritional deficiencies, whereby the patient desires essential nutrients. Interestingly, food urges has been identified as one of the strongest predictors of weight regain[51].

Food intolerance and aversion. Beyond food portions and preferences, some food items may be harder to tolerate, which may lead to the avoidance of specific food groups. Consequently, food intolerance and aversion may contribute to the reduced micronutrient intake after bariatric surgery[52]. Given its subjective nature, research on dietary intolerance varies widely due to differences in the applied definition of intolerance and the given research methodology[53–65]. In general, most reported intolerances are bread, cereals, dairy, fibrous vegetables, meat, pasta and rice[52]. Some of these intolerances may impose a risk on diet quality. For instance, avoidance of red meat may imply a lower iron intake, whereas other intolerances may improve diet quality by avoiding specific food items[66]. For instance, dumping syndrome may restrain patients from consuming energy-dense food items after surgery. The ingestion of refined sugar and fat triggers an exaggerate release of gut hormones (especially GLP-1) and the rapid entry of water into the intestinal lumen. This phenomenon of post-prandial hyperinsulinaemic hypoglycaemia is characterised by the occurrence of non-specific symptoms including a broad spectrum of presentations related to Whipple's triad for hypoglycaemia (e.g. symptomatic hypoglycaemia, documented low plasma glucose level, and resolution of symptoms after glucose administration). For hypoglycaemia, symptoms are categorised as autonomic (e.g. sweating, tremor and palpitation) or neuroglycopenic (e.g. confusion, weakness, light-headedness, dizziness, blurred vision, disorientation and eventually loss of consciousness)[67–69]. From a patient's perspective, dumping syndrome has been described as an unpleasant protection mechanism to avoid the consumption of energy-dense food items[70]. The effect on micronutrient intake may be rather small as energy-dense foods are often poor in micronutrient content[71]. Overall, food tolerance improves over time after both sleeve gastrectomy and Roux-en-Y gastric bypass[56–60,62,63]. On the basis of these individual physiological responses, efforts should be made to work towards personalising dietary recommendations based on physiological and tolerance response.

Non-compliance with dietary and supplementation recommendations. Another nutritional aspect that negatively affects nutrient intake is non-compliance with dietary recommendations and follow-up[72,73]. Dietetic counselling and nutritional supplementation is recommended to prevent nutritional complications after bariatric surgery[74,75]. However, the majority of research on non-compliance focuses on dietary recommendations and Roux-en-Y gastric bypass[76,77]. Regarding nutritional supplementation, non-compliance is frequently encountered in clinical practice. A recent systematic review and meta-analysis observed that guideline compliance rate for nutritional supplementation does not exceed 20% after bariatric surgery[78]. However, research indicates that supplementation compliance is associated with more favourable biochemical assessments of nutritional status[79,80]. Previously, increasing age and medicine intake were identified as positive predictors of compliance.

https://doi.org/10.1017/S0954422422000221 Published online by Cambridge University Press

Table 1. Micronutrient intake after bariatric surgery

Reference	Subjects	Methodology	Surgery	**Nutrient intake**[1]	Timepoints	**Findings**[2–4 and 5]
Bavaresco *et al.*[31]	48 patients (41 F, 7 M)	24-h dietary recall	RYGB	Dietary iron	Before and 1, 3, 6, 8 and 12 months after surgery	A significant reduction was observed starting from one month and dietary iron intake remained below recommended levels (non-defined) until 12 months after surgery.
Chou *et al.*[32]	40 patients (30 F, 10 M)	Food frequency questionnaire	SG	Dietary calcium, folate, iron, vitamins A, B_1, B_2, B_3, C and E and zinc	5 years after surgery	Dietary intake was lower than the Taiwan dietary reference intake (DRI) and ASMBS recommendations for all micronutrients at 5 years after surgery.
Colossi *et al.*[33]	210 patients (147 F, 63 M)	24-h dietary recall	RYGB	Dietary calcium, iron and vitamins A, B_1, B_2, B_3, B_5, B_6, B_9, B_{12} and C	Before and 1, 3, 6, 9, 12, 18 and 24 months after surgery	Dietary intake increased over time but was not regular. When comparing to the DRI (non-defined), the intake of vitamins A, B_1, B_3, B_5, B_6, B_9 and C was inadequate.
Cominetti *et al.*[34]	24 patients (20 F, 4 M)	3-d dietary record	RYGB	Dietary zinc	Before and 2 months after surgery	Dietary zinc intake decreased significantly after surgery. When comparing with the estimated average requirements (EAR) of the Institute of Medicine (IOM), 56% and 31% of the patients had a sufficient intake before and after surgery, respectively.
De Torres Rossi *et al.*[35]	44 patients (44 F, 0 M)	4-d dietary record	RYGB	Dietary vitamins A, B_{12}, C and E	3 years after surgery	Dietary vitamin B_{12} intake was significantly lower in the surgery group compared with controls. Dietary vitamin A and E intake was below the EAR of the IOM, while dietary vitamin A, E and C intake was below the recommended dietary allowance (RDA) of the IOM after surgery.
Freire *et al.*[36]	100 patients (84 F, 16 M)	24-h dietary recall	RYGB	Dietary calcium, folate, iron, vitamin B_1, vitamin B_{12} and zinc	Three groups: - 1: up to 2 years - 2: from 2 to 5 years - 3: over 5 years	Dietary micronutrient intake was similar among the three groups but was below the DRI (non-defined).
Gesquiere *et al.*[37]	54 patients (33 F, 21 M)	3-d dietary record	RYGB	Dietary and total copper, iron, vitamin B_{12}, vitamin C and zinc	Before and 1, 3, 6 and 12 months after surgery	Mean dietary intake was significantly decreased at 1 month. Afterwards, there was a gradual increase until 12 months, while remaining below baseline values at each timepoint. Compared with EAR of the IOM, the percentage of patients with an inadequate total intake was the highest 1 month after surgery.
Leiro *et al.*[38]	36 patients (36 F, 0 M)	Food frequency questionnaire	RYGB	Dietary calcium, iron, vitamin B_{12} and D	1 year after surgery	Dietary iron, calcium and vitamin D intake was inadequate in comparison with the RDA of the IOM.
Merchachita *et al.*[39]	60 patients (39 F, 21 M)	24-h dietary recall	RYGB	Dietary calcium, folate, iron and vitamin B_{12}	Before and 1 and 2 years after surgery	Dietary iron, folate and vitamin B_{12} intake decreased significantly after 1 year, but increased again after 2 years although not significant. No significant differences were found for calcium. More than 65% of the patients did not reach the DRI (non-defined) for calcium, iron and vitamin B_{12} at 1 and 2 years after surgery.
Miller *et al.*[40]	17 patients (16 F, 1 M)	4-d dietary record	RYGB	Dietary calcium, copper, folate, iron, magnesium, vitamins A, B_1, B_2, B_6, B_{12}, C, D, E and K and zinc	Before and 3 weeks and 3, 6 and 12 months after surgery	Dietary intake was highest at baseline and lowest at 3 weeks, while increasing by 12 months. During follow-up, the percentage of participants not meeting the EAR or AI (non-defined) generally increased. Vitamin D intake had the highest number of participants not meeting the requirements. At 1 year, more than 50% of the patients had an intake below the requirements for vitamins C, D and E, folate, calcium and magnesium.
Moizé *et al.*[41]	355 patients (267 F, 88 M)	3-d dietary record	SG and RY-GB	Dietary calcium, iron and magnesium	Before and 3, 6, 12, 18, 24, 30, 36, 48 and 60 months after surgery	Mean dietary intake was below the DRI (non-defined) of the IOM. The proportion of patients with an intake below the DRI varied throughout follow-up (calcium: SG 75–90%, RYGB 79–92%; magnesium: SG 87–100%, RYGB 87–99%; iron: SG 42–88%, RYGB 48–79%).
Netto *et al.*[42]	26 patients (22 F, 4 M)	Food frequency questionnaire	RYGB	Total vitamin C	Before and 12 and 24 months after surgery	A significant lower intake of total vitamin C was observed at 12 months (−16·46% ± 3·32%) and at 24 months (13·66% ± 9·82%) after surgery compared with before surgery.

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Table 1. (*Continued*)

Reference	Subjects	Methodology	Surgery	Nutrient intake[1]	Timepoints	Findings[2–4 and 5]
Novais *et al.*[43]	141 patients (141 F, 0 M)	24-h recall during 2 d	RYGB	Total calcium, folate iron, magnesium vitamins A, B_1, B_2, B_3, B_6, B_{12}, C and E and zinc	2–7 years after surgery	The probability of inadequate total intake was highest for calcium, folate, magnesium, vitamin C and vitamin E based on the EAR or AI of the IOM.
Riedt *et al.*[44]	25 patients (25 F, 0 M)	3-d dietary record	RYGB	Dietary and total calcium, magnesium and vitamins D and K	Before and 6 months after surgery	Dietary calcium intake decreased significantly after surgery, but total calcium intake remained similar after surgery. No difference was observed for magnesium, vitamin D or vitamin K.
Wardé-Kamar *et al.*[45]	69 patients (64 F, 5 M)	24-h dietary recall	RYGB	Dietary calcium, folate, iron and vitamin B_{12}	At least 18 months after surgery	Dietary iron and vitamin B_{12} intake was at or above the RDA (not defined), while dietary calcium and folate intake was 68 ± 47% and 61 ± 37% of the recommendations, respectively.

Abbreviations: AI, adequate intake; ASMBS, American Society for Bariatric and Metabolic Surgery; DRI, dietary reference intake; EAR, estimated average requirements; IOM, Institute of Medicine; RDA, recommended dietary allowance; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

Legend: [1]Dietary intake refers to micronutrient intake from food, while total intake refers to micronutrient intake from food and nutritional supplements.; [2]Adequate intake refers to a recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate.; [3]Dietary reference intake refers to a set of nutrient-based reference values that can be used for planning and assessing diets.; [4]Estimated average requirements refers to the average daily intake value that is estimated to meet the nutrient requirements in 50% of the individuals in a particular life stage and gender group.; [5]Recommended dietary allowance refers to the average daily intake value that is estimated to meet the nutrient requirements in 97–98% of the individuals in a particular life stage and gender group.[46]

While experiencing barriers was identified as a negative predictor of compliance. Most common barriers for supplement use are forgetfulness, price of supplements and experience of side effects[81].

Immediate and underlying determinants: gastrointestinal tract

Nutrient bioavailability refers to 'the efficiency with which a dietary component is used systemically through normal metabolic pathways'. It covers every step from the release of the nutrient, digestion, absorption, distribution, deposition, metabolic and functional use up to its excretion[82]. The gastrointestinal tract with its defined anatomy and physiology is responsible for the first steps from the release up to nutrient absorption across the length of the small intestine[83]. One might assume that the anatomical alterations of bariatric surgery affect digestion and absorption and contribute to the increased risk of developing nutritional deficiencies after bariatric surgery.

The 'bariatric' gastrointestinal tract at a glance. Traditionally, the presence of nutritional deficiencies after bariatric surgery was solely attributed to the mechanical aspects of inducing 'restriction' and 'malabsorption'. However, this mechanical hypothesis does not provide an adequate explanation for why some nutritional deficiencies are equally common after sleeve gastrectomy and Roux-en-Y gastric bypass[41,84]. In theory, it is plausible to assume that the drastic anatomical alterations of bariatric procedures influence gastrointestinal physiology. In turn, the anatomical and supposed physiological alterations imposed by the different types of bariatric procedures define the type and extent of nutritional deficiencies[85]. An overview of potential physiological alterations is visualised in Fig. 3 and reviewed elsewhere[21].

The ability of the gastrointestinal tract to digest food and absorb nutrients might be compromised by the profound anatomical and physiological alterations of bariatric surgery. Regarding digestion, the stomach needs an acidic environment for the initiation of macronutrient digestion (e.g. pepsinogen activation for protein digestion) and optimising micronutrients for absorption (e.g. releasing vitamin B_{12} from protein, optimising calcium and iron solubility and reducing ferric iron into the absorbable ferrous form)[86]. It is plausible that the resection and bypass of the oxyntic glands of the stomach affects digestion and nutrient absorption after surgery. In addition, this may as well reduce gastric secretion of intrinsic factor and, as such, affect vitamin B_{12} absorption further on in the ileum[87]. Moreover, a reduced gastric mixing and accelerated gastric emptying delivers partially undigested nutrients rapidly into the small intestine. This could delay protein, carbohydrate and lipid digestion until the ingested food reaches the pancreatic and biliary fluids that only appear in the common limb after Roux-en-Y gastric bypass. As a consequence, malabsorption of fat-soluble vitamins can occur that in turn affect other nutrients (e.g., vitamin D–calcium interaction). Beyond delaying digestion, a major area for nutrient absorption with transporters is bypassed after Roux-en-Y gastric bypass as visualised in Fig. 4. Altogether, changes in

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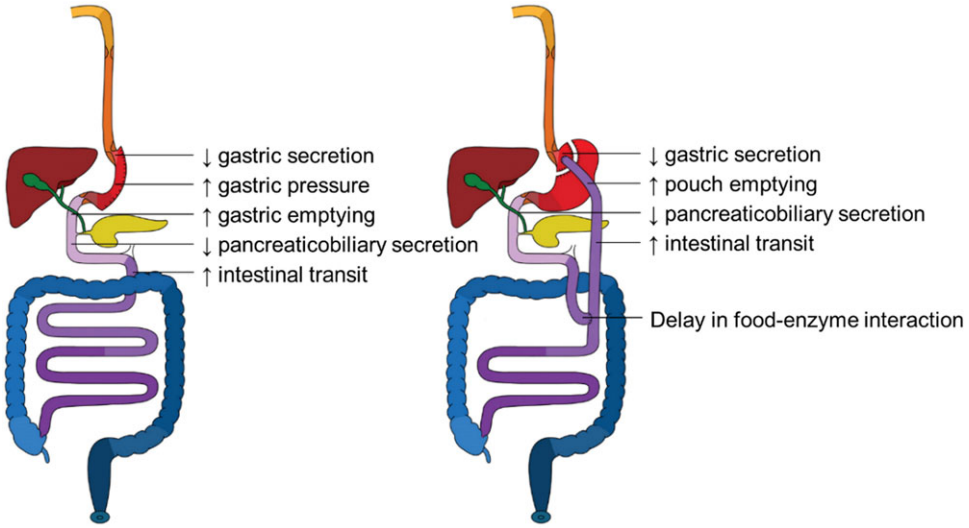

Fig. 3. Potential physiological alterations of sleeve gastrectomy (left) and Roux-en-Y gastric bypass (right).

gastrointestinal physiology have serious implications for digestion and nutrient absorption.

Immediate and underlying determinants: patients' medical history and therapy

When facing an abnormal biochemical parameter, micronutrient blood levels should be interpreted with special attention to the patient's medical history and treatment regimen. In particular, the presence of concomitant drug intake may complicate biochemical interpretation. Various drugs can affect a patient's nutritional status by affecting the nutrikinetic properties of a micronutrient or by intervening in the transport pathway of the nutrient[88,89]. From a nutrikinetic perspective, drugs can interfere with micronutrient absorption by (i) reducing gastric acid secretion, (ii) altering gastrointestinal motility or (iii) forming insoluble complexes. Additionally, drugs can affect the body's use and/or excretion of micronutrients. The proposed nutrikinetic mechanism of various drugs and their effect is summarised in Table 2[90,91]. Clinically relevant data on potential drug–nutrient interactions after bariatric surgery have not been explored so far. The effect of drug–nutrient interactions differs between patients but is generally more pronounced in patients on multiple or chronic treatment[88,90,92]. Therefore, the risk of potential drug–nutrient interaction should be recognised as a part of patient assessment after bariatric surgery due to the presence of persisting obesity-related comorbidities or complications that may require therapy. Beyond drug–nutrient interaction, the presence of inflammation in the context of infection, trauma or surgery is underrecognised as a potential confounder of biochemical micronutrient levels. However, it has been shown that inflammation may induce a redistribution of micronutrients from blood to other organs[29]. Consequently, decreased plasma micronutrient concentration is not necessarily an indication of micronutrient depletion or deficiency (e.g. vitamins A, B_6, C and D and zinc)[93]. On the contrary, inflammation can also increase micronutrient markers, meaning that a plasma micronutrient concentration within the reference range does not exclude the presence of micronutrient depletion or deficiency (e.g. iron)[93]. After bariatric surgery, clinical interpretation of plasma micronutrient concentration should therefore always be combined with C-reactive protein (CRP) as a surrogate marker of inflammation.

Enabling determinants: resources

To ensure maximal benefits and minimal complications, strict adherence to pre-operative screening and post-operative lifelong follow-up is pivotal after bariatric surgery. Pre-operative care should include an intake consultation with the surgeon, an internist, dietitian and psychologist, who gather (e.g. medical and psychosocial history) and provide information (e.g. bariatric procedures, benefits and risks). Different pre-surgical assessments are recommended including but not limited to physical examination and biochemical blood analysis. Post-operative surgery care differs in the early and late phases. A peri-operative enhanced recovery clinical pathway should be implemented in all patients who undergo a bariatric procedure, followed by rigorous lifelong follow-up on a regular basis[74,75,95]. Cancer research indicates that a multidisciplinary approach results in more beneficial treatment outcomes, but evidence for bariatric surgery patients is still lacking[96]. Besides a multidisciplinary approach, lifelong follow-up is advised. Depending on the type of bariatric procedure and length of follow-up, non-compliance ranges between 3% and 63%[97]. Nonetheless, follow-up visits provide the patient with a medical support network, the opportunity to detect nutritional deficiencies early on and a check-up of their dietary regimen[98]. Consequently, evidence indicates that post-bariatric patients have more nutritional deficiencies when being non-compliant to follow-up compared with compliant patients[80]. Moreover, serious nutritional complications are more common in non-compliant patients than in patients with partial or perfect follow-up (hazard ratio (HR) 3·09; 95% CI 1·74–5·50)[99]. It is generally accepted that the financial impact of bariatric surgery is an important determinant of non-compliance. The financial resources needed for the multidisciplinary follow-up consultations with a dietitian and nutritional supplementation

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Table 2. Drug–nutrient interactions and their proposed mechanism[90,91]

Drug type	Proposed mechanism	Potential effect on micronutrient
Antacids	Reduced gastric acid secretion and chelating the substance	Reduced iron and folate absorption.
Fluoroquinolones	Formation of an insoluble complex	Reduced calcium, iron magnesium and zinc absorption.
Histamine H2 antagonists	Reduced gastric acid and intrinsic factor secretion	Reduced solubility and absorption of calcium, decreased absorption of iron, and decreased release of vitamin B_{12} bound to protein and absorption.
Laxatives	Increased gastrointestinal motility	Reduced mineral and fat-soluble vitamin absorption.
Loop diuretics	Increased urinary excretion	Increased urinary loss of calcium, magnesium and vitamin B_1.
Metformin	Inhibition of receptor-mediated endocytosis of the vitamin B_{12}-intrinsic factor complex	Reduced vitamin B_{12} absorption.
Metoclopramide	Increased gastrointestinal motility	Reduced minerals and fat-soluble vitamin absorption.
Proton pump inhibitors	Reduced gastric acid and intrinsic factor secretion	Reduced solubility and absorption of calcium, decreased absorption of iron, decreased release of vitamin B_{12} bound to protein and absorption.
Thiazides	Increased urinary excretion	Increased urinary loss of calcium, magnesium and vitamin B_1.
Tetracyclines	Formation of an insoluble complex	Reduced calcium, iron magnesium and zinc absorption.

can be seen as an obstacle for some patients[99]. Therefore, the development of micronutrient deficiencies after bariatric surgery would likely be prevented if follow-up care is reimbursed.

Nutritional complications in obesity and after bariatric surgery

Together, an inadequate diet, altered gastrointestinal tract and a patient's medical history may predispose post-bariatric patients to develop nutritional deficiencies. As micronutrients are essential, nutritional deficiencies can have severe consequences including haematological, musculoskeletal or neurological complications. Most patients experience mild symptoms, but serious and even life-threatening cases have been reported as well[101]. Severe nutritional complications occur at an incidence rate of 4·5 per 1000 person-years, which is similar to the incidence rate of surgical complications[102]. Despite being not as rare as generally believed, nutritional complications receive less research attention compared with surgical complications[103]. Current available screening and supplementation recommendations for the discussed micronutrients are summarised in Table 3[74].

Haematological complications

Nutritional anaemia is a common complication of bariatric surgery. The prevalence of anaemia ranges between 3·6% and 52·7% and 6·0% and 63·6% after sleeve gastrectomy and Roux-en-Y gastric bypass, respectively. These high rates of anaemia may reflect a variety of vitamin or mineral deficiencies but are predominantly the result of iron, vitamin B_{12} or folate deficiency. Less common causes involve copper (deficiency), zinc (excessive intake), vitamin A (deficiency) and vitamin E (deficiency)[94,104].

Iron deficiency. Microcytic and hypochromic erythrocytes are considered the hallmark finding of iron deficiency, which reduces the oxygen-carrying capacity of the erythrocytes[94]. Symptoms and signs of iron deficiency with/without anaemia include fatigue, lethargy, reduced concentration, dizziness, paleness, dry skin, dry hair, alopecia, koilonychia and atrophic glossitis, but can be asymptomatic as well[105]. A recent systematic review and meta-analysis observed that the risk of developing iron deficiency is comparable after sleeve gastrectomy and Roux-en-Y gastric bypass (relative risk (RR) 1·27; 95% CI 0·98–1·64; $P = 0·069$)[106]. Increased divalent metal transporter expression may increase the absorptive capacity of the remaining nutrient-exposed intestine to compensate for the bypassed biliopancreatic limb with its nutrient transporters after Roux-en-Y gastric bypass[107]. Iron status monitoring and daily nutritional supplementation is recommended independently of the type of procedure. In case of deficiency, oral supplementation should be increased or replaced by intravenous administration for patients with severe intolerance or refractory iron deficiency[74].

Vitamin B_{12} deficiency. Another frequent cause of nutritional anaemia is vitamin B_{12} or cobalamin deficiency. Given vitamin B_{12} body stores can last for 3–5 years, vitamin B_{12} deficiency usually only becomes clinically relevant several years after bariatric

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Table 3. Nutritional screening and supplementation recommendations after sleeve gastrectomy and Roux-en-Y gastric bypass[74]

	Biochemical screening	Preventive supplementation	Therapeutic supplementation
Calcium	Total calcium.	Oral therapy: 1200–1500 mg/d. Citrated supplements are recommended.	Oral therapy: 1200–1500 mg/d from citrated supplements.
Copper	Serum copper and ceruloplasmin.	Oral therapy: 2 mg copper per day. Copper gluconate or sulphate is recommended.	Oral therapy: 3–8 mg/d copper gluconate or sulphate until indices return to normal for a mild to moderate deficiency. Intravenous therapy: 3–4 mg intravenous copper per day for 6 d or until indices return to normal and neurologic symptoms resolve for a severe deficiency.
Folate	Erythrocyte folate and homocysteine.	Oral therapy: 400–800 μg/d or 800–1000 μg/d in women of child-bearing age.	Oral therapy: 1000 μg/d to achieve normal levels and then resume normal dosages to maintain levels.
Iron	Iron panel, complete blood count, total iron-binding capacity, ferritin and soluble transferrin receptor.	Oral therapy: 18–60 mg/d via multivitamins and supplements divided from calcium, acid-reducing drugs, and foods high in phytates or polyphenol. Ferrous sulphate, fumarate or gluconate is recommended.	Oral therapy: 150–200 mg/d via multivitamins and supplements divided from calcium, acid-reducing drugs, and foods high in phytates or polyphenol. Ferrous sulphate, fumarate or gluconate is recommended. Intravenous therapy: ferric gluconate or sucrose is recommended for patients with severe intolerance to oral iron or refractory deficiency.
Vitamin A	Serum vitamin A.	Oral therapy: 5000–10 000 IU/d.	Oral therapy: 10 000–25 000 IU/d in case of deficiency without corneal complications. Intramuscular therapy: 50 000–100 000 international units for 3 d, followed by 50 000 international units for 2 weeks in case of deficiency without corneal complications.
Vitamin B_1	Serum thiamine screening is recommended for high-risk groups.	Oral therapy: 50–100 mg/d. Thiamine from a B-complex supplement or high-potency multivitamin is recommended.	Oral therapy: 100 mg two to three times per day until symptoms resolve. Intravenous therapy: 200 mg three times per day to 500 mg once or twice daily for 3–5 d, followed by 250 mg/d for 3–5 d or until symptoms resolve, then consider treatment with 100 mg/d orally, indefinitely, or until risk factors have been resolved. Intramuscular therapy: 250 mg once daily for 3–5 d or 100–250 mg monthly.
Vitamin B_{12}	Serum methylmalonic acid with or without homocysteine.	Oral therapy: 350–1000 μg/d from a disintegrating tablet or liquid. Parenteral therapy: 1000 μg per month.	Oral therapy: 1000 μg/d to achieve normal levels and then resume normal dosages to maintain levels.
Vitamin D	25-Hydroxyvitamin D, parathyroid hormone, and bone formation and resorption markers.	Oral therapy: 2000–3000 international units of vitamin D titrated to therapeutic 25-dihydroxyvitamin D levels.	Oral therapy: vitamin D3 at least 3000 IU/d and as high as 6000 IU/d or 50 000 IU vitamin D2 one to three times per week.
Vitamin E	Serum vitamin E	Oral therapy: 15 mg/d.	Not defined.
Zinc	Serum and plasma zinc	Oral therapy: 8–22 mg/d for Roux-en-Y gastric bypass and 8–11 mg/d for sleeve gastrectomy.	Not defined.

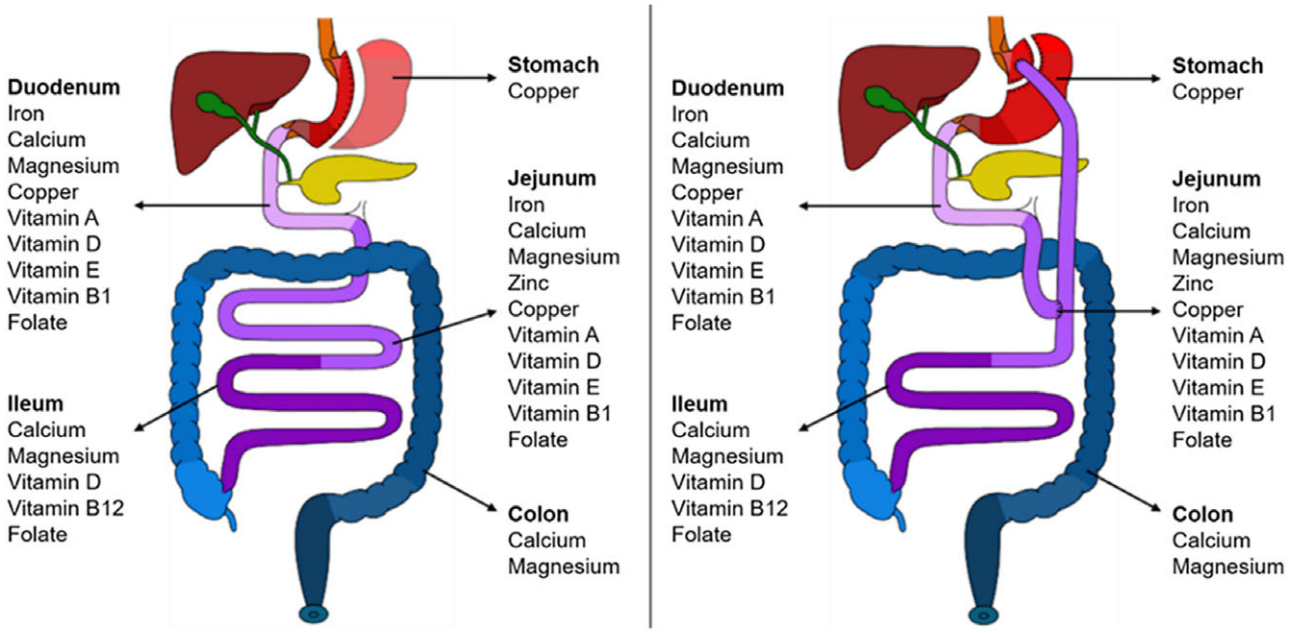

Fig. 4. Gastrointestinal micronutrient absorption after sleeve gastrectomy (left) and Roux-en-Y gastric bypass (right).

surgery[108]. Contrary to iron deficiency, the risk of post-operative vitamin B_{12} deficiency is higher after Roux-en-Y gastric bypass compared with sleeve gastrectomy (RR 1·86; 95% CI 1·15–3·02; $P = 0·012$)[106]. Severe vitamin B_{12} deficiency is characterised by macrocytic erythrocytes, leading to megaloblastic anaemia[109]. Symptoms and signs of vitamin B_{12} with/without anaemia resemble the symptoms of iron deficiency (anaemia) including fatigue and glossitis. Beyond haematological complications, vitamin B_{12} deficiency can contribute to neurological complications such as myelopathy, neuropathy, paraesthesia and ataxia. As the morphological features of vitamin B_{12} deficiency are camouflaged in case of iron deficiency and symptoms are similar, vitamin B_{12} status should always be monitored in combination with iron status[101,108,110].

Vitamin B_9 or folate deficiency. Although less common, folate deficiency is another potential cause of nutritional anaemia. Folate absorption can occur along the entire small intestine, which explains the low incidence of folate deficiency, especially when supplemented with folic acid. The risk of developing folate deficiency is comparable after sleeve gastrectomy and Roux-en-Y gastric bypass (RR 0·79; 95% CI 0·47–1·35; $P = 0·391$)[106]. Similar to vitamin B_{12}, severe folate deficiency is characterised by macrocytic erythrocytes that lead to megaloblastic anaemia[109]. Symptoms include weakness, anorexia and weight loss[108]. Considering the risk of neural tube defects in the foetus, it is advised that women who underwent a bariatric procedure receive between 400 and 1000 µg of folic acid in the periconceptional period[74,111].

Musculoskeletal complications

Calcium and vitamin D deficiency. Bone fragility has emerged as a common and severe complication of bariatric surgery. Different mechanisms have been proposed to contribute to bone fragility, including (i) micronutrient malabsorption, (ii) mechanical unloading and (iii) changes in sex, gut and adipose-derived hormones[112]. Among micronutrients, calcium and vitamin D are essential to ensure bone health. After surgery, malabsorption of calcium and vitamin D may cause a hypocalcaemic state. As a result, the parathyroid glands will secrete higher levels of parathyroid hormone. Under the control of parathyroid hormone, urinary calcium secretion is decreased and skeletal calcium is mobilised to maintain serum calcium[108,112]. In the short term, the clinical symptoms of calcium and vitamin D deficiency include muscle weakness, muscle cramps and back pain[108,113]. In the long term, bone loss can manifest and translate into fracture risk. Fracture risk seems to increase following mixed restrictive and malabsorptive bariatric procedures with a predominance of fractures at osteoporotic sites (RR 1·4–2·3 depending on the study). Mounting data indicate that fracture risk manifests in the long term, whereas bone remodelling already occurs within the first year after surgery[114,115]. To date, it remains unclear whether sleeve gastrectomy has the same effect on skeletal health as Roux-en-Y gastric bypass[116]. Due to the multifactorial skeletal effect of bariatric surgery, a multidisciplinary approach of screening and supplementation is recommended[117].

Neurological complications

A large spectrum of neurological complications can arise after bariatric surgery with an assumed prevalence between 1% and 16%. These complications are related to a variety of micronutrients that vary from time to presentation. In the short term, Wernicke's encephalopathy or acute polyradiculoneuropathy can arise. Long-term complications include optic neuropathy, myelopathy, peripherical neuropathy and myopathy[118].

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Prevention, recognition and management are crucial as most complications are reversible or improve over time under therapy.

Water-soluble vitamins B_1, B_9 and B_{12}. Vitamin B_1 or thiamine is an essential micronutrient for myelin formation in the nerve cells with limited body storage. Encephalopathy is a major nutritional complication of vitamin B_1 deficiency that mainly develops in the first week or first months after surgery. After surgery, inadequate dietary intake or vomiting can lead to depleted stores. In turn, severe thiamine deficiency results in selective neuronal cell death that can culminate into acute and chronic encephalopathy. Wernicke's encephalopathy is an acute neurological condition that is characterised by a triad of symptoms including ophthalmological problems, ataxia and consciousness disturbances. When left untreated, Wernicke's encephalopathy can progress to Korsakoff syndrome, which is characterised by a chronic state of mental dysfunction with permanent memory impairment[118]. In severe cases, thiamine deficiency may result in death[119]. Another rare complication associated with vitamin B_1 deficiency is acute polyradiculoneuropathy. It presents as pain in the lower limbs, followed by ascending paralysis, ataxia, areflexia and sensory loss, which resembles Guillain–Barré syndrome[120,121]. Although the risk of thiamine deficiency is highest in the first months after surgery, it can present lifelong, especially in combination with inadequate intake due to persisting vomiting and supplementation non-compliance or alcohol abuse[122]. In addition to thiamine, other water-soluble vitamins can result in neurological complications. Although uncommon, folate deficiency may lead to peripheral neuropathy or restless leg syndrome, while vitamin B_{12} deficiency can manifest neurologically by presenting as myelopathy, neuropathy, paraesthesia and ataxia[123].

Fat-soluble vitamins A and E. Given that fat-soluble vitamins require bile acids for absorption, deficiencies of fat-soluble vitamins with neurological manifestations may arise after bariatric surgery. Due to its role in photoreceptor function, vitamin A deficiency can result in optic neuropathy, xerophthalmia and night blindness[124,125]. Vitamin E is essential for normal neurological functioning and for protecting neural cell membranes from oxidative damage. After bariatric surgery, the clinical presentation of vitamin E deficiency is rarely documented. However, vitamin E deficiency may present as peripheral neuropathy, skeletal myopathy, gait disturbances, head titubation, decreased sensation, ataxia, ophthalmologic disorders and nystagmus[126].

Copper and zinc deficiency. Mineral and trace-element deficiencies have seldom been described after bariatric surgery. Although human cases are rare, copper deficiency can manifest neurologically as myelopathy and peripheral neuropathy after bariatric surgery[127], while zinc deficiency can manifest as a myeloneuropathy-like disorder with spastic gait and sensory ataxia[108].

Conclusion

Taken together, the pathological onset of nutritional deficiencies is not yet fully understood, but the immediate role of diet, the gastrointestinal tract and the medical state of the patient cannot be ignored. Financial resources needed for the multidisciplinary follow-up consultations with a dietitian and nutritional supplementation can be seen as an obstacle for some patients. These determinants predispose post-bariatric patients to develop nutritional deficiencies. As micronutrients are essential, deficiencies can have severe consequences, including haematological, musculoskeletal or neurological complications. Most patients present with mild symptoms, but serious and even life-threatening cases have been reported. Therefore, it is of the utmost importance to monitor the nutritional status of patients before and after bariatric surgery.

Acknowledgements

N.S. is supported by a KU Leuven research grant (C32/17/046). B.V.d.S. and T.V. received senior clinical research fellowships from FWO, the Flemish Research Council.

The authors report no conflicts of interest.

N.S. wrote the manuscript. All authors contributed to the manuscript, revised and approved the final version of the manuscript.

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