Endocrine and Metabolic Complications After Bariatric Surgery

11

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Hormones are powerful things, we are helpless in their wake

—Meg Cabot

Abbreviations

1,25(OH)2D	1,25Dihydroxy-vitamin D
25(OH)D	25-Hydroxy-vitamin D
ASBMS	American Society for Bariatric and Metabolic Surgery
BMI	Body mass index
BPD-DS	Biliopancreatic diversion with duodenal switch
EWL	Excess weight loss
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide-1
LAGB	Laparoscopic adjustable gastric banding
mg	Milligrams
mg/dL	Milligrams per deciliter
ng/mL	Nanograms per milliliter
NIPHS	Noninsulinoma pancreatogenous hypoglycemia syndrome
PCOS	Polycystic ovarian syndrome
PTH	Parathyroid hormone
RYGB	Roux-en-Y gastric bypass
SAGB	Single anastomosis gastric bypass

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SG	Sleeve gastrectomy
SHPT	Secondary hyperparathyroidism
T2DM	Type 2 diabetes mellitus
TSH	Thyroid stimulating hormone
VBG	Vertical banded gastroplasty
VIP	Vasoactive intestinal peptide

11.1 Introduction

Adipose tissue is not simply a site for energy storage. It is an active endocrine organ and a major regulator of metabolism. Adipocytes are endocrine cells. They release hormones, including leptin and adiponectin, which have effects on major organs that participate in the regulation of metabolism. Further, adipocytes have receptors for many hormones, including epinephrine and insulin, which allows for extensive cross-communication with other organs and subsequent effect on metabolic homeostasis [1].

In the right environment, susceptible individuals accumulate fat mass (***adiposity***). The outdated concept of overweight and obesity as defined by thresholds of body mass index has given way to a more contemporary view. With adiposity there are changes to function and structure of adipocytes and adipose tissue (including vasculature, nerves, and connective matrix). Adipocytes, like any other cells in the body, may become diseased. Adipose tissue as a whole may become diseased too. Analogous to ophthalmopathy, cardiomyopathy, nephropathy, neuropathy, and encephalopathy, there is also ***adiposopathy***. Adiposopathy includes changes in adipocyte cytology and function, and changes in adipose tissue anatomy, distribution, and function, which then contribute to metabolic derangements (Table 11.1). Adiposopathy, or "sick fat," is an endocrine disease, and is the primary treatment target to correct the metabolic and endocrine derangements of overweight or obesity

Table 11.1 Anatomical and functional changes of adipose tissue in adiposopathy

Anatomical changes	Functional changes
Adipocyte hypertrophy Growth of adipose tissue beyond its vascular supply Increased number of adipose tissue immune cells • Macrophage ring structures surrounding dying adipocytes Ectopic fat deposition (in other body tissues) Heterogeneous adipose tissue distribution • Visceral adiposity linked to metabolic diseases	Impaired adipogenesis and adipocyte hypertrophy Adipocyte lipolysis in excess of lipogenesis • Increased free fatty acids Pathogenic adipose tissue endocrine responses • Hypoadiponectinemia • Hyperleptinemia Pathogenic adipose tissue immune responses • High levels of inflammatory markers Pathogenic crosstalk between fat and other organs

[2–5]. Bariatric endocrinology is the sub-sub-specialty of endocrinology that deals with adiposopathy as an endocrine disease [6].

Adiposopathy helps to explain why not all patients with adiposity develop metabolic and endocrine complications. Those individuals whose adipose tissue remains functionally intact with a gain in fat mass do not develop metabolic or endocrine complications. Conversely, individuals with adiposopathy are unable to compensate and have progression of disease. Cardiovascular events (i.e., myocardial infarction and cerebrovascular accident), and damage to other organs (i.e., hepatic cirrhosis from non-alcoholic steatohepatitis) are the ultimate complications of this disease process over time. It is optimal to intervene as early as possible in the natural history of adiposopathy (Fig. 11.1). Adiposopathy also explains why some individuals develop metabolic and endocrine derangements at varying degrees of adiposity.

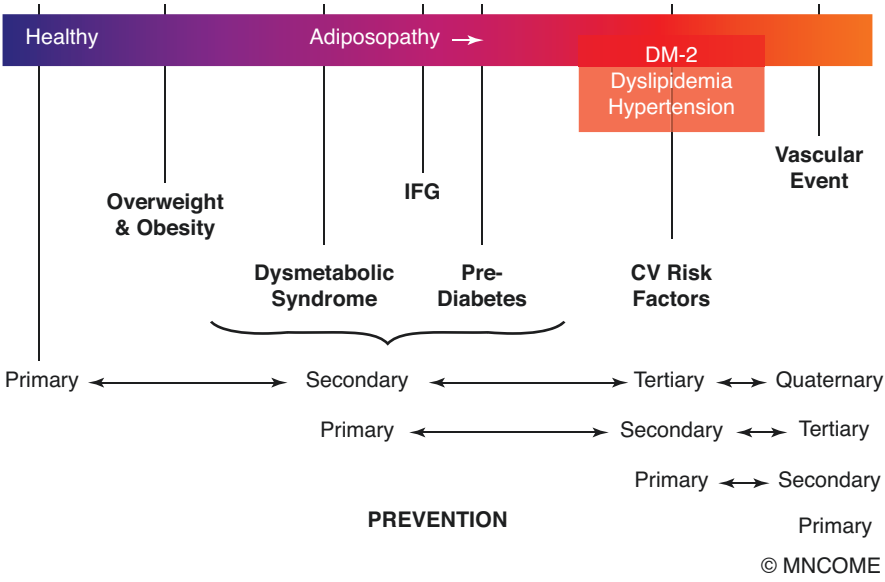

Fig. 11.1 Prevention of cardiovascular disease. The accumulation of fat mass leads to changes in adipose tissue function and the development of an inflammatory milieu. The top bar indicates the progression from healthy adipose tissue to progressively worsening adiposopathy. Adiposopathy is etiological in the progression of the disease processes that eventually lead to organ damage. A vascular event implies long-standing disease. Treating a patient after a vascular event makes this a primary intervention and represents a lack of prevention. Interventions to modify known cardiovascular risk factors as a primary intervention make treatment of vascular events secondary intervention. Interventions to modify the risk factors of the known cardiovascular risk factors make treatment of a vascular event a tertiary intervention. Early intervention to preserve a healthy lifestyle and prevent the development of overweight, obesity, and adiposopathy makes treatment of a vascular event a quaternary intervention. Early intervention prevents, or at least significantly delays a vascular event. The corollary to this is that primary prevention of vascular events starts with the implementation of a healthy lifestyle early in life. Abbreviations: *DM-2* type 2 diabetes mellitus, *IFG* impaired fasting glucose, *MNCOME* Minnesota Center for Obesity, Metabolism and Endocrinology, PA. © Copyright Minnesota Center for Obesity, Metabolism and Endocrinology, PA (MNCOME)

The best approach to the management of overweight, obesity, and adiposopathy is to regard them as any other chronic disease. Chronic diseases may be treated, managed, and controlled. They may go into remission. Chronic diseases, however, are not curable. Each patient needs to understand that weight management, and monitoring for complications of the disease continuum, are both for life. Treatment should be individualized and designed to address the duration and severity of disease [6–8].

Most patients accomplish effective weight loss with medical treatment. Bariatric surgery should be reserved for patients whose disease is refractory to medical management, and the burden of disease warrants a more aggressive approach [9]. Referral to bariatric surgery must underscore that this is not a cure for overweight, obesity or adiposopathy. Patients need to understand that the benefit of bariatric surgery carries implicit risks.

Bariatric surgery improves the endocrine and metabolic derangements that develop with weight gain and adiposopathy (Table 11.2) [10]. Bariatric surgery is also an effective treatment for the medical problems that result from overweight, obesity, and adiposopathy (Table 11.3) [11]. Treatment for adiposopathy, overweight, or obesity should be ongoing after bariatric surgery. Most patients need re-intervention with pharmacotherapy to prevent weight regain, and to promote weight loss beyond what surgery may provide. Chapter 21 addresses weight regain after bariatric surgery.

Life-long monitoring of patients for the development of complications of bariatric surgery is required. In addition, monitoring for the development or re-development of the underlying complications of overweight, obesity, and adiposopathy is also necessary. As an example, in the United Kingdom by the end of 7 years of follow-up, 4.3% of bariatric surgery patients and 16.2% of matched controls had type 2 diabetes mellitus (T2DM). The incidence of T2DM was 28.2 per 1000 person-years in controls and 5.7 per 1000 person-years in bariatric surgery patients. The adjusted hazard ratio was 0.20 (95% CI 0.13–0.30, $p < 0.0001$) [12]. The weight loss and metabolic improvements achieved with bariatric surgery significantly decreased the risk of diabetes, but did not eliminate it. Chapter 22 addresses this subject further.

This chapter will address endocrine and metabolic complications of bariatric surgery. This chapter will not address endocrinology and metabolism subjects dealt with in other chapters of this textbook. (Nutritional deficiencies are covered in Chap. 23, and reproductive complications are covered in Chap. 15).

11.2 Incidence of Endocrine and Metabolic Complications of Bariatric Surgery

The incidence of endocrine and metabolic complications following bariatric surgery varies widely. The type of bariatric surgery procedure, and the time elapsed after the procedure, each determine the incidence of endocrine and metabolic complications. Malabsorptive procedures are more likely to cause endocrine problems than

Table 11.2 Changes in metabolic parameters with the bariatric procedures most commonly done

	Procedure			
	Malabsorptive	Restrictive		Mixed
	Bilio-pancreatic diversion duodenal switch	Adjustable gastric banding	Vertical sleeve gastrectomy	Roux en-Y gastric bypass
Excess weight loss	82%	44%	66%	50%
Mean weight loss	30–40%	15–30%	20–30%	25–35%
BMI change	−18	−7.1	−10.9	−16.7
Diabetes remission	98%	59%	81%	78%
Dyslipidemia remission	99%	36%	67%	61%
Hypertension remission	83%	56%	78%	66%
Energy expenditure	n/a	↓	↓	↑
Ghrelin	↓↓	↓→↑	↓↓	↓→↑
Glucagon like peptide-1	↑	→↓	↑	↑
Peptide YY	↑	↑	↑	↑
Oxyntomodulin	↑	→	↑	↑
GIP	↓	→	→↑	↓→↑
Cholecystokinin	n/a	n/a	→	→
Pancreatic polypeptide	↓	→	→	→
Amylin	n/a	→	→	↓
Glucagon secretion	↑	n/a	n/a	↓→↑
Postpandial insulin secretion	↑	→↓	↑	→↓
Hepatic insulin sensitivity	↑	↑	↑	↑
Muscle insulin sensitivity	↑	↑	↑	↑
Plasma glucose	↓	↓	↓	↓
Hemoglobin A1c	↓3.8%	↓1.8%	↓2.9	↓2.9%
Glucose effect	Weight-independent	Weight-dependent	Weight-independent	Weight-independent
Triglycerides	↓	↓	↓	↓
LDL-C	↓	↓↑	↓	↓
HDL-C	→	→	↑	↑
Visceral fat mass (Waist circumference)	↓	↓	↓	↓
Resistin	n/a	↑	↓	→
Leptin	↓	↓	↓	↓
Adiponectin	↑	↑	→	↑
Leptin to adiponectin ratio	↓	↓	↓	↓
Thyroid hormone requirements	↓	↓	↓	↓
Testosterone levels in men	↑	↑	↑	↑
Estrogen to testosterone ratio in women	↑	↑	↑	↑

Multiple arrows denote equivocal data

BMI body mass index, *GIP* glucose-dependent insulinotropic polypeptide, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *n/a* no data available

Table 11.3 Outcomes of bariatric surgery on metabolic, endocrine, and atherosclerotic diseases

Obesity-related endocrine disease	Outcome after bariatric surgery
Cardiovascular disease	82% risk reduction
Diabetes mellitus, type 2	82–98% resolved
Dyslipidemia	63% resolved
Dysmetabolic syndrome	80% resolved
Gout	72–77% resolved
Hirsutism in women	75–79% resolution
Hypertension	52–92% resolved
Mortality from diabetes mellitus, type 2	92% reduction
Mortality from heart disease	56% reduction
Non-alcoholic fatty liver disease	37% resolution
Polycystic ovarian syndrome	100% resolution of menstrual irregularity

restrictive procedures. It is not possible to predict which individual patient may develop endocrine problems after a bariatric procedure. Therefore, regardless of the published incidence data, reviewed below, each patient needs a pre-operative assessment of glycemia, calcium and bone metabolism, thyroid function, and the gonadal axis. Each patient also needs education, best delivered by a team of healthcare professionals, so there is a clear understanding of the benefits and risks of bariatric surgery, including endocrine and metabolic complications. After bariatric surgery, education and monitoring are necessary on an ongoing basis [13].

Nutritional and vitamin deficiencies in patients after malabsorptive surgeries develop from lack of adherence to meal planning and nutritional supplementation recommendations over time [9]. Nutritional deficiencies are the subject of Chap. 5.

11.2.1 Incidence of Derangements of Calcium Metabolism

Vitamin D deficiency is prevalent throughout the world [14]. In Boston, Massachusetts, USA, serum 25-hydroxyvitamin D (25(OH)D) plasma concentrations of 30 nanograms per milliliter (ng/mL) or less, are found in 64% of healthy adults. One-third of adults have 25(OH)D levels of 20 ng/mL or less [15]. Decreased intestinal calcium absorption due to vitamin D deficiency causes a drop in the plasma calcium concentration. The parathyroid hormone (PTH) plasma concentration goes up secondary to the drop in plasma calcium. Eucalcemia is maintained by the multiple actions of elevated PTH, which makes secondary hyperparathyroidism common and actual hypocalcemia less common.

Derangements of calcium metabolism are prevalent in patients who have had bariatric surgery. In 80 patients who had surgery in France, 10 years after biliopancreatic diversion with duodenal switch (BPD-DS) 78% of the patients maintain a BMI < 35. At the same 10-year mark, vitamin D levels are normal in 35.4% of patients, the rest having low levels. The low level of vitamin D coupled with a short gut and hindered calcium absorption causes secondary hyperparathyroidism (SHPT)

in 62% of patients [16]. A study of 1436 Canadian patients had similar results, where 68.6% of patients had SHPT 5 years after BPD-DS [17]. The prevalence of SHPT was higher than the prevalence of low vitamin D, which reached a plateau at 15.5% 36 months after surgery. This is a strong indicator that the decreased length for absorption of the gut plays a major role in the development of SHPT, regardless of vitamin D status. The prevalence of hypocalcemia was 26.9% 2 years after surgery [17].

Data on 1470 patients who had bariatric surgery in Taiwan shows that the overall prevalence of SHPT is 21.0% before bariatric surgery [18]. Multivariate analysis shows that vitamin D level is the only independent predictor of SHPT before surgery. The prevalence of SHPT increases after bariatric surgery.

- 1 year after surgery the prevalence of SHPT is:
  - 35.4% overall
  - 50.6% for One anastomosis gastric bypass (OAGB)
  - 33.2% for Roux-en-Y gastric bypass (RYGB)
  - 25.8% for laparoscopic adjustable gastric banding (LAGB)
  - 17.8% for sleeve gastrectomy (SG)
- 5 years after surgery the prevalence of SHPT is:
  - 63.3% overall
  - 73.6% for SAGB
  - 56.6% for RYGB
  - 38.5% for LAGB
  - 41.7% for SG

Serum PTH at 1 year after surgery correlated with decreased BMI and weight loss. Multivariate analysis showed that age, sex, calcium level, and bypass procedure were independent predictors of SHPT after surgery [18].

11.2.2 Incidence of Bone Density Loss and Fracture Risk

Weight loss causes bone mineral density loss [19–21]. Following bariatric surgery, this bone mineral density loss places patients at higher risk for fractures [22]. In Olmsted County, Minnesota, USA, with a median follow-up of 7.7 years, 79 subjects from a cohort of 258 patients who had bariatric surgery between 1985 and 2004, had 132 fractures. This represented a 2.3-fold increase in fracture risk [23]. In Quebec, Canada, 12,676 patients who had bariatric surgery between 2001 and 2014 had a higher risk of fracture compared to control patients with obesity after a mean of 4.4 years of follow-up. Fracture risk was highest after BPD-DS [24].

Taken together, the prevalence of hypovitaminosis D, hypocalcemia, SHPT, bone mineral density loss, and increased fracture risk warrant an aggressive approach to the preservation of calcium homeostasis and bone integrity in patients with obesity who have bariatric surgery.

11.2.3 Incidence of Hypoglycemia

On the other hand, the incidence of hypoglycemia is much lower. In a Swedish nationwide cohort of 5040 patients who had gastric bypass surgery between 1986 and 2006, the incidence of hypoglycemia was as low as 0.2%. The rate of hospitalization for hypoglycemia and other related diagnoses, including confusion, syncope, epilepsy, and seizures was two- to sevenfold higher in gastric bypass patients, compared to matched controls. There was no hypoglycemia after vertical banded gastroplasty (VBG) or LAGB. The absolute risk of hypoglycemia in this study underestimates the incidence of hypoglycemia because it excluded outpatient episodes from the analysis [25].

In a study at Catholic University in Rome, 120 patients were randomized 1:1 to RYGB or SG and followed for a year. Of these, 117 patients (93%) completed the 12-month follow-up. Reactive hypoglycemia was detected in 14% of SG patients and 29% of RYGB patients ($p = 0.079$) [26]. Daily hypoglycemic episodes during continuous glucose monitoring did not differ between groups ($p = 0.75$). Four of 59 RYGB subjects (6.8%) had 1–3 hospitalizations for symptomatic hypoglycemia. There were no hospitalizations for hypoglycemia in patients who had an SG [26].

The incidence of hypoglycemia at the Geisinger Health Systems was studied in a cohort of 1206 patients without preoperative diagnoses of T2DM or hypoglycemia [27]. One-hundred fifty eight patients had a diagnosis of hypoglycemia, a glucose less than 60 milligrams per deciliter (mg/dL), or documentation of the use of medications to treat hypoglycemia (13%). Only 8 of the 158 patients had severe hypoglycemia, defined as a glucose of <40 mg/dL, need for emergency room care, or hospitalization. This is the only study to date that documented that hypoglycemia risk over 5 years after surgery is higher in patients whose preoperative hemoglobin A1c was under 5.5%, body mass index (BMI) was under 39 kilograms per meter^2 (kg/m^2), and percent of excess weight loss (EWL) was 75% or more [27].

11.2.4 Incidence of Derangements of the Thyroid Axis

Weight loss after bariatric surgery causes a fall in the thyroid-stimulating hormone (TSH) level, which reflects a decreased need for thyroid hormone [28–33]. Patients with hypothyroidism requiring treatment with thyroid hormone need a reduction of the thyroid dose after bariatric surgery.

11.2.5 Incidence of Changes in the Gonadal Axis

Overweight, obesity, and adiposopathy impair fertility in both men and women [34, 35]. Bariatric surgery improves fertility and increases the likelihood of an unintended pregnancy [36–38]. In 2016, the Centers for Disease Control included bariatric surgery within the past 2 years as a risk for adverse health events in pregnancy [39]. There is no data on the prevalence of undesired pregnancy after bariatric surgery.

Table 11.4 Endocrine complications of malabsorptive weight loss surgeries (Roux-en-Y, sleeve gastrectomy, biliopancreatic diversion, and biliopancreatic diversion with duodenal switch)

Endocrine complication	Highest prevalence	Testing needed	Monitoring frequency
Vitamin D deficiency	64%	25-Hydroxyvitamin D	Baseline, every 2 months until stable, and then annually
Hypocalcemia	27%	Total plasma calcium Total protein Phosphorus 24-h urinary calcium	Baseline, every 2 months until stable, and then annually
Secondary hyperparathyroidism	74% at 5 years	Parathyroid hormone	Baseline, every 2 months until stable, and then annually
Metabolic bone disease	30%	DEXA scan	Baseline, yearly until stable, then every 2 years
Reactive hypoglycemia	29%	Mixed meal glucose tolerance test Glucose (fingerstick) CGMS if available	As needed
Severe hypoglycemia with neuroglycopenia	7%	Glucose and c-peptide during episode	As needed
Increased fertility (may lead to undesired pregnancy)	Not reported	Log of menses (women) Total testosterone (men)	Baseline and annually
Decreased thyroid hormone requirements in patients with corrected hypothyroidism	100%	Free T3, Free T4, TSH	Baseline, every 6 weeks until stable, and then annually

Abbreviations: *DEXA* dual energy X-ray absorptiometry, *CGMS* continuous glucose monitoring system, *T3* triiodothyronine, *T4* tetraiodothyronine, *TSH* thyroid stimulating hormone

11.3 Adverse Endocrine and Metabolic Sequelae After Bariatric Surgery

Table 11.4 lists the major endocrine and metabolic complications of bariatric surgery. Disorders of glycemia and calcium metabolism are more likely after malabsorptive procedures. All bariatric procedures lead to increased fertility and decreased thyroid hormone requirements.

11.4 Pathophysiology of the Enlisted Adverse Sequelae

11.4.1 Pathophysiology of Calcium and Bone Metabolism

Calcium intake is frequently inadequate to meet calcium needs after bariatric surgery [40].

Bariatric procedures that decrease the receptive capacity of the stomach will result in decreased exposure of ingested calcium salts to the acid of the stomach. This is especially so following RYGB, where most of the stomach is removed from the alimentary canal. The acidity of the stomach contributes to the solubilization of calcium salts, and bypassing the stomach contributes to calcium malabsorption [41–43].

Bariatric procedures that result in a shortened alimentary canal limit the absorptive capacity of the gut for calcium. In addition to a decreased absorptive surface, there is also a shortened time for absorption to happen. Competition for absorption with other cations further decreases calcium absorption. Coupled with the prevalent hypovitaminosis D, calcium absorption from the intestine decreases [44–46]. Figure 11.2 illustrates the major mechanisms involved in the decreased intestinal calcium absorption following malabsorptive bariatric surgeries.

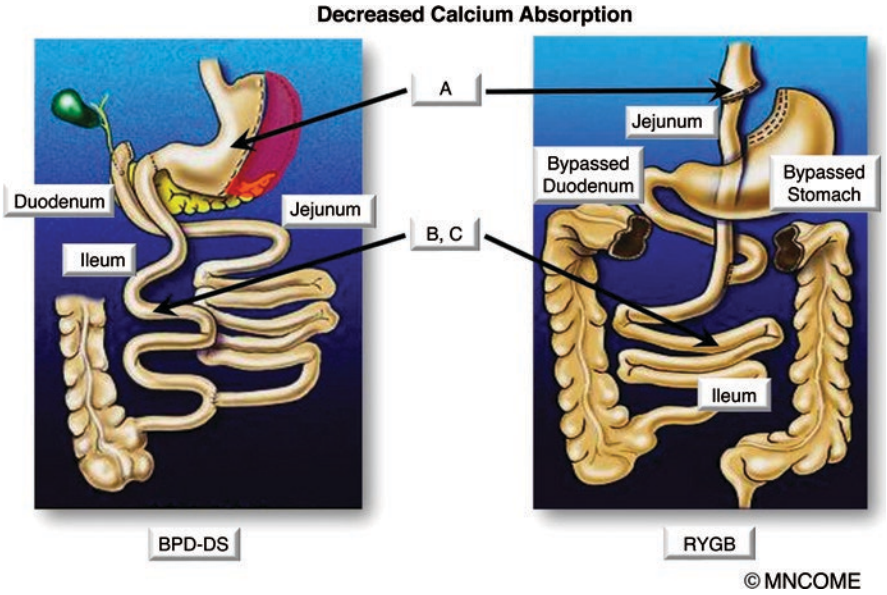

Fig. 11.2 Decreased calcium absorption after malabsorptive procedures. Following bariatric surgery calcium absorption is impaired. The red area in the left panel represents the partial gastrectomy that is part of the BPD-DS procedure. The major mechanisms involved are (**a**) decreased gastric acid exposure limiting solubilization of calcium salts; (**b**) decreased length of small intestine for absorption of calcium (including competing cation absorption), also leading to a decreased time for calcium absorption; and (**c**) decreased activity of 1, 25-dihydroxy-vitamin D. Additionally, most patients have inadequate calcium intake over time. Abbreviations: *BPD-DS* biliopancreatic diversion with duodenal switch, *RYGB* Roux-en-Y gastric bypass, *MNCOME* Minnesota Center for Obesity, Metabolism and Endocrinology, PA. © Copyright Minnesota Center for Obesity, Metabolism and Endocrinology, PA (MNCOME)

Hypocalcemia due to decreased intestinal calcium absorption stimulates the secretion of PTH from the parathyroid glands, resulting in SHPT [17, 18, 47, 48]. SHPT returns the plasma calcium concentration to normal. The effects of SHPT include increased calcium reabsorption from the renal tubules, with an associated phosphaturic effect. In addition to returning calcium to the circulation directly, the lower plasma phosphate decreases the formation of calcium phosphate, increasing the plasma calcium indirectly. SHPT also leads to increased activity of the renal hydroxylase that converts 25(OH)D to 1,25 dihydroxy-vitamin D ($1,25(OH)_2D$). Through the activation of vitamin D, SHPT indirectly increases intestinal calcium absorption [49].

SHPT causes increased bone resorption, which frees calcium from bone stores. Over time, continuous bone resorption accelerates bone mineral density loss and increases fracture risk [21, 49–51]. The development of primary hypogonadism, leading to the menopause, worsens the bone mineral density loss in women after bariatric surgery [52]. The use of contraception that suppresses gonadal function leading to estrogen deficiency (i.e., progesterone only products), should be avoided in premenopausal women after bariatric surgery.

Figure 11.3 Summarizes the pathophysiology of calcium metabolism after bariatric surgery.

11.4.2 Pathophysiology of Glucose Metabolism

Immediately after RYGB, before a patient with T2DM experiences weight loss, first-phase insulin secretion, and hepatic insulin sensitivity increase [53]. Blood glucose levels drop within 48 h after SG and RYGB [54]. Patients with insulin-requiring T2DM prior to surgery have an 87% reduction in their total daily insulin requirements by postoperative day 2 [55]. These dramatic changes in glycemia, irrespective of fat mass, are due to multiple effects of bariatric surgery (Table 11.2). Patients have an increased risk of hypoglycemia after malabsorptive bariatric surgeries.

The dumping syndrome, which affects more than 15% of patients after bariatric surgery, includes the following symptoms:

- Abdominal cramping and diarrhea
- Nausea and vomiting
- Flushing
- Hypotension
- Tachycardia
- Lightheadedness (and syncope)

The dumping syndrome occurs following the ingestion of simple carbohydrates without the anatomy to slow absorption (i.e., bypassing the pyloric sphincter) [56, 57]. Sugar in the small intestine causes an osmotic overload and fluid shifts into the

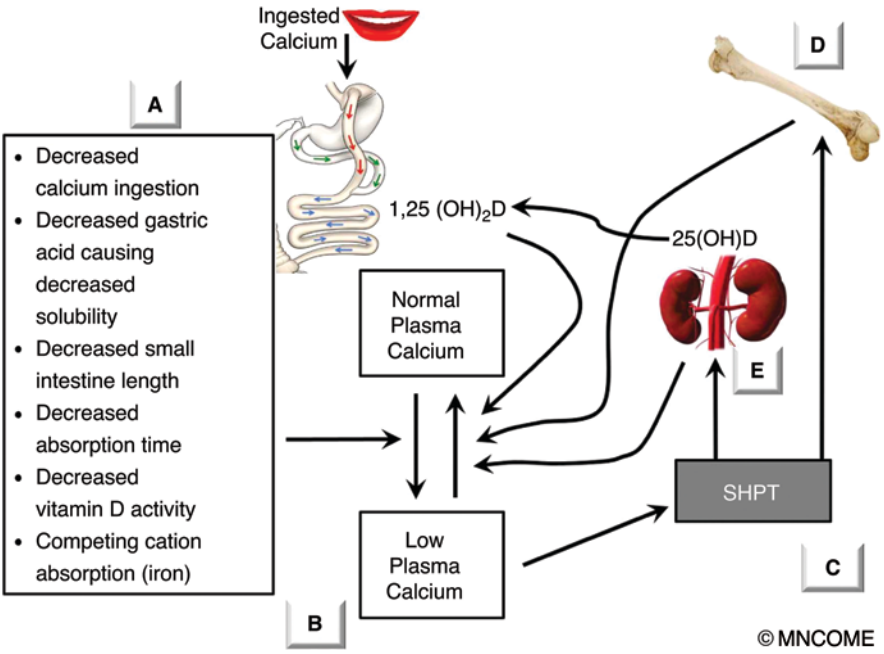

Fig. 11.3 Pathophysiology of derangements of calcium metabolism. Following bariatric surgery, there are significant changes to calcium homeostasis. (**a**) Intestinal absorption of calcium is decreased. (**b**) This causes a fall in the plasma calcium. (**c**) Hypocalcemia stimulates the secretion of parathyroid hormone, which will return calcium levels to normal. (**d**) SHPT increases bone resorption, freeing calcium into the circulation. Over time this causes bone mineral density loss (osteomalacia). (**e**) In the kidneys parathyroid hormone increases calcium reabsorption and promotes phosphaturia. This adds to the plasma calcium directly, and indirectly by lowering the mass effect of phosphate on calcium. Parathyroid hormone increases the activity of the renal hydroxylase that converts 25(OH)D to the activated 1,25(OH)2D. Activated vitamin D increases intestinal calcium absorption, which adds to the plasma calcium. Abbreviations: *1,25 (OH)2D* 1,25 Dihydroxy-vitamin D, *25(OH)D* 25-hydroxy-vitamin D, *SPTH* secondary hyperparathyroidism, *MNCOME* Minnesota Center for Obesity, Metabolism and Endocrinology, PA. © Copyright Minnesota Center for Obesity, Metabolism and Endocrinology, PA (MNCOME)

intestinal lumen leading to watery diarrhea. The small intestine releases vasoactive intestinal peptide (VIP), gastric inhibitory polypeptide (GIP), and glucagon-like peptide-1 (GLP-1) in response to the presence of nutrients in the gut. These enteric hormones vasodilate the splanchnic vessels drawing volume away from the peripheral circulation. A decrease in peripheral circulating volume is the cause of the tachycardia and eventual hypotension [56, 58]. This "early dumping syndrome" is common after RYGB and generally occurs within minutes to 1 h after the ingestion of calorie-dense foods, especially refined sugars and fats [59].

Postprandial or reactive hypoglycemia is part of the dumping syndrome. [56–58, 60, 61] The small intestine releases GIP and GLP-1. As elevated glucose levels reach the pancreatic islets, they stimulate the beta cells to release insulin. GLP-1 boosts the release of insulin. Both insulin and GLP-1 inhibit glucagon release from

the alpha cells, which are downstream in the islet circulation. The result is an exaggerated insulin release in excess of need. Insulin levels remain high even as glucose levels go down past normal. This hyperinsulinemic hypoglycemia is clinically manifested about 1–3 h after meal ingestion and usually develops months to years after surgery [26, 62–64]. The American Society for Bariatric and Metabolic Surgery (ASBMS) issued a position statement on this subject in 2017. In contrast to the "early dumping syndrome," hyperinsulinemic hypoglycemia is what historically was termed "late dumping syndrome."

Severe hypoglycemia after bariatric surgery is uncommon. In this situation, patients develop neuroglycopenia, which can cause cognitive impairment, loss of consciousness, or seizures 1–3 h after ingesting simple carbohydrate [65–67]. Neuroglycopenia is not present when fasting, and this is a distinction from patients with insulinoma where fasting hypoglycemia is common [68]. Neuroglycopenia may occur in association with physical activity and is associated with hypoglycemia unawareness due to loss of adrenergic and cholinergic symptoms [59].

Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) includes neuroglycopenic symptoms and mimics the clinical presentation of insulinoma. However, neuroglycopenia develops 2–4 h after ingestion of meals, and imaging studies of the pancreas are negative for a pancreatic mass. Histologically, the pancreas in these patients shows islet hypertrophy and nesidioblastosis [68, 69].

11.4.3 Pathophysiology of the Thyroid Axis

A healthy hypothalamic–pituitary–thyroid axis adjusts thyroid hormone production to meet needs. Patients with a normal thyroid axis prior to surgery are ensured a continued euthyroid state.

Autoimmune thyroiditis is common and therefore it is the most common thyroid problem in patients who undergo bariatric surgery. For most patients their disease is evolving. The stage of thyroid gland destruction determines the need to replace thyroid hormone at the time of bariatric surgery. One-fifth of patients undergoing bariatric surgery already require thyroid hormone replacement [28]. The scant literature on thyroid function after bariatric surgery is consistent in documenting a drop in TSH [32, 70]. The pathophysiology behind this observation is not yet defined.

11.4.4 Pathophysiology of Gonadal Axis

A discussion of the pathophysiological changes of the gonadal axis with obesity or with bariatric surgery is beyond the scope of this chapter, and is complex [34, 35]. Men with hypogonadotropic hypogonadism due to obesity will return their gonadal axis to normal after bariatric surgery. Women with polycystic ovarian syndrome (PCOS; which is largely due to adiposopathy and insulin resistance affecting ovarian function), or with hypogonadotropic hypogonadism due to obesity, will return to

normal after bariatric surgery. For both men and women, there is increased fertility after surgery.

11.5 Diagnosis

In 2008, we authored the first guideline for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric patient [71]. This was a joint effort of the American Association of Clinical Endocrinologists and the American Society for Metabolic and Bariatric Surgery. The newest revision of the guideline is now available and is a valuable reference to have along with this textbook.

11.5.1 Diagnosis of Derangements of Calcium and Bone Metabolism

All patients should have baseline measurements of total calcium, total protein, 25(OH)D, phosphorus, and PTH prior to any malabsorptive procedure (Table 11.4) [9]. We recommend close monitoring of 25(OH)D, total calcium (with concomitant total protein), phosphorus, and PTH every 2 months until PTH levels are normalized on two consecutive draws. Patients should then be encouraged to maintain their calcium and vitamin D intake, and repeat measurements may then be made annually.

A baseline measurement of bone mineral density with dual-energy X-ray absorptiometry (DEXA) should be done prior to any malabsorptive procedure. Any subsequent DEXA scans should be done on the same densitometer, by the same technician if possible, to allow for direct comparisons to baseline [72, 73]. A repeat DEXA scan 1 year after surgery establishes which patients have had rapid bone loss, and would require close observation over time [72, 73].

11.5.2 Diagnosis of Derangements of Glucose Metabolism

All patients undergoing bariatric surgery should have baseline hemoglobin A1c, fasting glucose, and fasting insulin or c-peptide levels documented. Glycemic measures should be part of the ongoing management of all patients because some will develop or redevelop hyperglycemic derangements [12]. Patients with symptoms of hypoglycemia should be tested for this (Table 11.4).

Any patient who had a malabsorptive procedure, who now has symptoms consistent with reactive hypoglycemia, but not neuroglycopenia, should be provided with a glucose meter. Self-monitoring of capillary glucose by fingerstick sampling and food logging provides documentation of the temporal relationship of meals to symptoms, and the level of glycemia with symptoms. For most patients with postprandial hyperinsulinemic hypoglycemia medical nutrition therapy (MNT) will correct the symptoms [59, 65, 74].

Patients who have persistent symptoms despite nutritional intervention should undergo a mixed meal glucose tolerance test. Testing should be done in a facility

with expertise, where personnel are prepared to assist any patient who develops severe hypoglycemia during the test period. Although the mixed meal contains protein, carbohydrate, and fat, the carbohydrate content is not standardized. Most mixed meal tests will include 40–75 g of carbohydrate [75, 76].

The conventional oral glucose tolerance test, where a patient ingests 75 g of soluble glucose and plasma glucose is measured at intervals up to 4 h post ingestion, is not recommended in patients who had malabsorptive bariatric surgery. The glucose load may precipitate the dumping syndrome during testing and is otherwise not well tolerated [75].

Where insulinoma or NIPHS is suspected, patients should be admitted to the hospital for observation and testing. Whipple's triad is:

1. The presence of neuroglycopenia
2. A concomitant low plasma glucose (less than 50 mg/dL)
3. Resolution of the symptoms with glucose treatment [77–79]

Patients who meet the criteria for Whipple's triad are considered to have verified hypoglycemia, and an etiology for it should be defined. NIPHS is a diagnosis of exclusion (factitious or iatrogenic causes, dumping syndrome, and insulinoma are excluded). Plasma glucose is required to avoid the pitfalls of capillary testing. A c-peptide level should always be drawn with the plasma glucose [80, 81].

Imaging of the pancreas is needed to exclude an insulinoma. This includes an ultrasound of the pancreas (transabdominal, endoscopic, and/or intraoperative), and computerized tomography with thin slices through the pancreas. Negative imaging excludes insulinoma. Selective calcium stimulation of the arterial supply of the pancreas helps define a gradient of insulin release, and can guide a partial pancreatectomy to ameliorate symptoms in NIPHS [82].

11.5.3 Diagnosis of Derangements of the Thyroid Axis

All patients undergoing bariatric surgery should have baseline thyroid function tests documented, including free T3, free T4, and thyroid-stimulating hormone (TSH). In patients with a family history of thyroid disease, or with a goiter on physical examination, we recommend documentation of thyroid peroxidase and thyroglobulin antibodies. Pre-existing thyroid abnormalities of structure or function should lead to closer follow-up of the thyroid status of these patients after surgery (Table 11.4) [83].

11.5.4 Diagnosis of Derangements of the Gonadal Axis

All patients undergoing bariatric surgery should have a thorough sexual history documented. If there is sexual dysfunction a baseline set of gonadal hormones should be done.

11.6 Management

A multidisciplinary team approach results in the best care of patients with adiposopathy, overweight, or obesity [6, 8, 84–86]. This holds true for patients whose disease warrants bariatric surgery [11, 13]. The team approach to patient care ensures that patients receive the knowledge they need to make decisions about their health, and that options are discussed at a level that is educationally, linguistically, and culturally appropriate for each patient. MNT is essential to good outcomes in bariatric surgery patients. The team should include registered dieticians, nurse educators/coaches, psychologists, and physicians or physician extenders [6]. A major goal is to maintain patient engagement, to avoid sequelae of bariatric surgery, or complications that develop over time, that may go undiagnosed and untreated.

11.6.1 Management of Derangements of Calcium and Bone Metabolism

The prevalence of SHPT makes it necessary to monitor and adequately supplement vitamin D and calcium in all patients who have had bariatric surgery, especially malabsorptive procedures [16, 18]. Calcium citrate supplementation allows for better absorption of calcium than calcium carbonate in the absence of gastric acid [87]. The total daily elemental calcium dose from all sources for patients who had BPD-DS is 1800–2400 mg. For all other patients, the total daily elemental calcium dose from all sources is 1500 mg [9, 72]. Calcium supplementation in multiple daily doses that add up to the needed total daily elemental calcium dose is necessary. Large oral doses at once overcome the absorptive capacity of the gut for calcium and result in the passage of the ingested calcium without absorption. The goal of treatment is to optimize intestinal calcium absorption to avoid the development of SHPT [87, 88].

Oral bisphosphonates are contraindicated in patients who had a malabsorptive procedure with a stomach resection because they require the acidity of the stomach for absorption. They are contraindicated in patients who had a restrictive procedure because the tablets may cause ulcerations. Intravenous bisphosphonate therapy should be considered for patients with documented bone mineral density loss [72, 83]. Other treatments for low bone mineral density may be considered as needed (i.e., denosumab). Consideration should be given to the use of estrogen replacement in women who transition to a postmenopausal state (primary hypogonadism) as a means to preserve bone mineral density.

11.6.2 Management of Derangements of Glucose Metabolism

MNT for patients after bariatric surgery is best provided by registered dieticians with expertise in overweight, obesity, adiposopathy, and the metabolic and

endocrine complications of the various bariatric procedures. MNT should include recommendations for meals with low-carbohydrate, low-glycemic index, adequate protein, and heart-healthy fats. Patients should restrict alcohol and caffeine intake. Most patients with post-bariatric surgery hypoglycemia will respond to MNT [59, 83, 89].

Continuous glucose monitoring is now an important tool in the management of patients with hypoglycemia after bariatric surgery. Self-awareness of the glucose level in response to meals helps most patients modify their meal plan to prevent hypoglycemia [90–92].

Pharmacological interventions that help treat hypoglycemia from NIPHS after bariatric surgery include [93, 94]:

- Decreased glucose absorption from the intestine by blockade of intestinal disaccharidases.
  - acarbose, 50–100 mg three times a day, with each meal, [94, 95]
- Inhibition of insulin release from the beta cells in the pancreas
  - diazoxide, 50 mg two times a day, [96]
  - octreotide, 100 mcg two times a day, subcutaneously, [97–99]
  - calcium channel blockers (i.e., verapamil, 80 mg two times a day; nifedipine, 120 mg/day), [95, 100]
- Modulation of insulin release by the beta cells in the pancreas
  - GLP-1 receptor agonists, (i.e., liraglutide, 1.2–1.8 mg a day, subcutaneously) [101].

Gastric feeding through a gastric tube placed into the gastric remnant reverses the hypoglycemia in NIPHS, and has been advanced as a treatment option. This also serves to document that nutrient delivery alterations are the major cause of NIPHS, and not a change in pancreatic islet mass [102].

Reversal of the bariatric procedure should be done for any patient who continues to have neuroglycopenia that cannot be managed medically. This is mostly applicable to patients who had RYGB. Since reversal of RYGB effectively cures hypoglycemia, this also favors a non-pancreatic cause of severe hypoglycemia [103, 104]. Therefore, partial or total pancreatectomy should be reserved for rare recalcitrant cases [59, 68, 81, 83].

11.6.3 Management of Derangements of the Thyroid Axis

Thyroid function should be followed closely in all patients with pre-existing thyroid disease. Levothyroxine dosing needs adjustments to normalize TSH values, and to keep the TSH at the low end of its reference range. It is expected that weight loss will decrease thyroid needs, and the dose of levothyroxine will need to be adjusted down. However, many patients will have progression of their autoimmune thyroiditis over time, with loss of endogenous thyroid hormone production. The levothyroxine dose will need to be increased in these patients. Decreased absorption of

levothyroxine in malabsorptive procedures is possible. Liquid forms of levothyroxine may improve absorption after malabsorptive procedures, and benefit patients with swallowing difficulties after bariatric surgery [83]. Softgel levothyroxine may also be considered for these patients [83].

11.6.4 Management of Derangements of the Gonadal Axis

Women with overweight or obesity, of reproductive age with intact anatomy, should be advised that their fertility status will improve with weight loss and correction of adiposopathy. Bariatric surgery could lead to an unintended pregnancy, and counseling to prevent this is necessary [83]. Women with PCOS reach bariatric surgery with years of irregular or absent menses. They will resume normal menses after bariatric surgery, and should be prepared to deal with them.

Men with pre-existing hypogonadotropic hypogonadism have a rise in the circulating testosterone with weight loss and reversal of adiposopathy. This translates into increased libido and improved erectile function after bariatric surgery. Men should be counseled about these changes, and be forewarned about possible unintended pregnancy.

Key Points

- *Bariatric endocrinology deals with derangements of structure and function of the adipocyte as an endocrine cell, and adipose tissue as an endocrine organ. In addition to adiposity, overweight and obesity lead to adiposopathy. Adiposopathy then contributes to derangements of metabolism that are the complications of this disease.*
- *Weight loss, in addition to reducing adiposity, treats adiposopathy. This is true both with medical and surgical weight loss.*
- *Bariatric surgery is an effective treatment of overweight, obesity, and adiposopathy in patients whose disease is refractory to medical management.*
- *Bariatric procedures carry a significant risk of metabolic and endocrine complications, which falls under the scope of practice or bariatric endocrinology. SHPT and NIPHS are two situations where a bariatric endocrinology team should be included in the care of patients.*
- *All patients with overweight, obesity, and adiposopathy benefit from a team approach to medical care that includes ongoing medical nutrition therapy, coaching to achieve effective behavior modification for a healthier lifestyle, and pharmacotherapy to treat complications of surgery but also to allow for ongoing weight loss beyond what surgery can accomplish.*

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