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SURGERY FOR OBESITY AND RELATED DISEASES

ASMBS Guidelines/Statements, Part 2

Lipids and bariatric procedures
Part 2 of 2: scientific statement from the American Society for Metabolic and Bariatric Surgery (ASMBS), the National Lipid Association (NLA), and Obesity Medicine Association (OMA)[1]

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Abstract Bariatric procedures generally improve dyslipidemia, sometimes substantially so. Bariatric procedures also improve other major cardiovascular risk factors. This 2-part Scientific Statement examines the lipid effects of bariatric procedures and reflects contributions from authors representing the American Society for Metabolic and Bariatric Surgery (ASMBS), the National Lipid Association (NLA), and the Obesity Medicine Association (OMA). Part 1 was published in the Journal of Clinical Lipidology, and reviewed the impact of bariatric procedures upon adipose tissue endocrine and immune factors, adipose tissue lipid metabolism, as well as the lipid effects of bariatric procedures relative to bile acids and intestinal microbiota. This Part 2 reviews: (1) the importance of nutrients (fats, carbohydrates, and proteins) and their absorption on lipid levels; (2) the effects of bariatric procedures on gut hormones and lipid levels; (3) the effects of bariatric procedures on

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[1]Before 2016, the Obesity Medicine Association was the American Society of Bariatric Physicians.

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nonlipid cardiovascular disease (CVD) risk factors; (4) the effects of bariatric procedures on lipid levels; (5) effects of bariatric procedures on CVD; and finally, (6) the potential lipid effects of vitamin, mineral, and trace element deficiencies, that may occur after bariatric procedures. (Surg Obes Relat Dis 2016;12:468–495.)

Keywords: Adiposopathy; Bariatric procedures; Bariatric surgery; Cardiovascular disease; Cholesterol; Dyslipidemia; Gastrointestinal hormones; Micronutrients; Nutrition; Obesity; Vitamins

Bariatric procedures generally improve dyslipidemia, sometimes substantially so. Part 1 of this 2-part scientific statement provided an overview of: (1) adipose tissue, cholesterol metabolism, and lipids; (2) bariatric procedures, cholesterol metabolism, and lipids; (3) endocrine factors relevant to lipid influx, synthesis, metabolism, and efflux; (4) immune factors relevant to lipid influx, synthesis, metabolism, and efflux; (5) bariatric procedures, bile acid metabolism, and lipids; and (6) bariatric procedures, intestinal microbiota, and lipids, with specific emphasis on how the alterations in the microbiome by bariatric procedures influence obesity, bile acids, and inflammation, which in turn may all affect lipid levels.

Part 2 of this scientific statement reviews: (1) the importance of nutrients (fats, carbohydrates, and proteins) and their absorption on lipid levels; (2) the effects of bariatric procedures on gut hormones and lipid levels; (3) the effects of bariatric procedures on nonlipid cardiovascular disease (CVD) risk factors; (4) the effects of bariatric procedures on lipid levels; (5) effects of bariatric procedures on CVD; and finally (6) the potential lipid effects of vitamin, mineral, and trace element deficiencies that may occur after bariatric procedures.

Bariatric procedures, intestinal nutrient metabolism, and lipids

General nutritional considerations

Bariatric procedures may affect gut hormones, which are important for nutrient digestion and metabolism, which in turn may affect lipid levels. Both the quantity and quality of foods (e.g., fats, carbohydrates, proteins, vitamins, minerals, trace elements, and other chemical compounds) can influence adipocyte and adipose tissue function. Metabolic diseases (including dyslipidemia) [1–3] are affected by bariatric procedures.

Fats are organic compounds that include cholesterol (see Part 1 of this Scientific Statement) and triglycerides. Triglycerides are composed of 3 fatty acids attached to a glycerol backbone, which may be saturated (no double bonds) or unsaturated (1 or more double bonds). The fatty acid components of triglycerides are mostly 4–28 carbons long. In adipose tissue, stored triglycerides usually have fatty acid components 12–24 carbons long and 0–6 double bonds. The fatty acids perhaps most easily mobilized from adipocytes by hormone-sensitive lipase are fatty acids that are shorter and more unsaturated (e.g., highly mobilized fatty acids include 16–20 carbon fatty acids with 4–5 double bonds; weakly mobilized fatty acids include 20–24 carbon fatty acids with 0–1 double bond) [4]. Dietary fats are energy-dense foods, with fat generating 9 calories per gram, carbohydrates 4 calories per gram, proteins 4 calories per gram, and alcohol 7 calories per gram. After undergoing emulsification by bile secreted by the liver and gallbladder, most dietary fats are absorbed in the small intestine.

Carbohydrates are chain or ring structures composed of 1 carbon per 2 hydrogens per 1 oxygen and include: (1) simple sugars often utilized for short-term cellular energy (i.e., monosaccharides such as glucose, fructose, and galactose, as well as disaccharides such as sucrose, maltose, and lactose); (2) complex carbohydrates for intermediate energy storage (i.e., plant starches composed of long polymers of glucose molecules with bond attachments in the same direction, and animal glycogen composed of polymers of glucose molecules with branching structure); and (3) polysaccharide cellulose composed of long polymers of glucose molecules with bond alternating in opposite directions, which provides structural support for plant cell walls and which represent "dietary fiber." After enzymatic digestion of complex carbohydrates beginning in the mouth, and after further metabolism occurring in the small intestine, simple sugars are absorbed in the small intestine. In humans, dietary fiber usually passes through the intestine without significant digestion. As noted in Part 1 of this Scientific Statement, certain bacteria microbiota (e.g., phyla Firmicutes) can at least partially digest fibers into short chain fatty acids, which may be absorbed by the intestine, thus enhancing body energy/calorie absorption [5].

Proteins are linear chain compounds, folded into a tertiary or quarternary structure composed of nitrogen-containing amino acids. After undergoing digestion in the stomach by gastric juices, proteins are absorbed in the small intestine as amino acids. Different proteins may differ in their effects on adipocyte function and insulin secretion [1].

Dietary quantity can affect lipid blood levels [2,3,6,7]. Especially in patients with dyslipidemia caused by adiposopathic consequences of obesity, fat weight loss may be the most important factor in improving dyslipidemia, relative to

the types of nutrients consumed. At least within the first year or so, regarding food quality: (1) Restricting saturated fats and transfats may reduce low-density lipoprotein (LDL) cholesterol levels; (2) restricting carbohydrates (especially carbohydrates with high glycemic index and load) may reduce triglyceride and increase high-density lipoprotein (HDL) cholesterol levels; and (3) if substituted for simple carbohydrates and saturated/transfats, increasing the proportion of protein food intake may: (a) improve adipocyte and adipose tissue function, (b) increase satiety and promote thermogenesis, (c) preserve muscle mass, particularly in older individuals, (d) favorably affect metabolic parameters, and (e) improve dyslipidemia [1,3,8,9]. To the extent bariatric procedures alter the quantity and quality of intestinal nutrient absorption [10], then alterations in macronutrients and micronutrients may affect lipid levels. Therefore, to better understand how bariatric procedures might affect metabolic disease such as dyslipidemia, it is important to understand nutrient metabolism. Part 1 of this Scientific Statement provided details regarding the clinical relevance of enzymes, systemic hormones, inflammation mediators, and other factors relative to adipocyte and adipose tissue function, and the effect of bariatric surgery on these factors with respect to dyslipidemia. The following background discussion on nutrient digestion and metabolism in this Part 2 specifically focuses on the effects of bariatric procedures on gut hormones (Fig. 1; Table 1) [3,11–53] and how affected gut hormones may influence lipid blood levels.

Intestinal fat metabolism

More than 90% of consumed fats are triglycerides. Upon entering the small intestine, dietary fats stimulate duodenal cholecystokinin release (Fig. 1; Table 1) [3,11–53], facilitating bile release from the gallbladder and liver, as well as lipase, cholesteryl esterase, and phospholipase release from the pancreas. After triglycerides undergo emulsification by bile salts, pancreatic and intestinal lipases hydrolyze the triglycerides. Digested triglycerides are absorbed into the small intestine as free fatty acids and monoglycerides in the duodenum, with a small fraction absorbed as free glycerol and diglycerides. Once absorbed in intestinal cells, free fatty acids and glycerol are re-esterified into triglycerides and then packaged with re-esterified cholesterol into apoB48-containing chylomicrons. Chylomicrons enter mesenteric lymph vessels and eventually are introduced into the circulation, where they bind to peripheral tissues such as membranes of hepatocytes, adipocytes, and myocytes. Increased hepatic delivery of triglyceride-containing saturated fatty acids or trans-fatty acids may result in hepatosteatosis, and increased very low density lipoprotein (VLDL) secretion, potentially resulting in hypertriglyceridemia [54]. It is unclear that hepatic delivery of monounsaturated fats increase hepatosteatosis or VLDL secretion. Polyunsaturated omega-3 fatty acids may actually decrease hepatosteatosis and may decrease hepatic VLDL secretion, reducing triglyceride levels [55].

During periods of fasting, when body tissue energy is needed, triglycerides stored in adipocytes undergo lipolysis by hormone-sensitive lipase, generating the release of free or nonesterified fatty acids in to the circulation, which are complexed and carried by plasma proteins (i.e., albumin). Free fatty acids are the major secretory product of adipose tissue. Once these circulating free fatty acids are delivered to tissues such as muscle and liver, they may become activated in the intracellular cytosol by binding to coenzyme A, wherein they are then transported to the mitochondria via carnitine, undergo β-oxidation, and ultimately generate acetyl-CoA. Acetyl-CoA enters the tricarboxlic acid cycle (i.e., citric acid cycle or Krebs cycle) to generate adenosine triphosphate, which is the intracellular transporter of chemical energy.

Two of the more sentinel lipases involved with fat metabolism include hormone-sensitive lipase and lipoprotein lipase. Hormone-sensitive lipase is an intracellular, rate-limiting enzyme highly expressed in adipocytes that hydrolyzes cholesteryl esters to free cholesterol and hydrolyses triglyceride esters into free fatty acids and diglycerides. Adipocyte triglyceride lipase also hydrolyzes triglycerides; adipocyte triglyceride lipase and hormone-sensitive lipase are responsible for more than 95% of triglyceride hydrolase activity in white adipose tissue [3]. Diglycerides are rapidly metabolized by diglyceride lipase to a monoglycerides, with the remaining fatty acid cleaved from the glycerol backbone by monoglyceride lipase. Hormone-sensitive lipase is the lipolytic enzyme most affected by hormones. Hormone-sensitive lipase is downregulated by insulin hormone, with hyperinsulinemia being anabolic in promoting triglyceride storage in adipocytes. Conversely, hypoinsulinemia increases hormone-sensitive lipase activity, catalyzing intracellular triglycerides into fatty acids. Hormone-sensitive lipase is also upregulated with catecholamines (i.e., β-adrenergic stimulation) and adrenocorticotropic hormone (ACTH). Increased stress responses via sympathetic nervous system and ACTH and decreased insulin levels are thus both catabolic in promoting triglyceride breakdown and, ultimately, facilitating adipose tissue release of fatty acids into the circulation.

Lipoprotein lipase is another important lipase enzyme that is produced and secreted by adipocytes into extracellular surroundings. Lipoprotein lipase serves to hydrolyze triglycerides found in circulating lipoproteins into glycerol and free fatty acids. Because adipocytes do not synthesize fatty acids, adipocytes rely on acquiring extracellular fatty acids generated by lipoprotein lipase interaction with lipoproteins for intra-adipocyte lipogenesis. In the postprandial state, lipoprotein lipase interacts with chylomicrons (as well as other triglyceride-rich lipoproteins, such as VLDL and intermediate-density lipoproteins [IDL]). In the fasting state, lipoprotein lipase mainly interacts with VLDL and other triglyceride-rich lipoproteins. Once extracellular triglycerides are hydrolyzed by lipoprotein lipase, free fatty acids undergo transport via fatty acid transport protein into adipocytes.

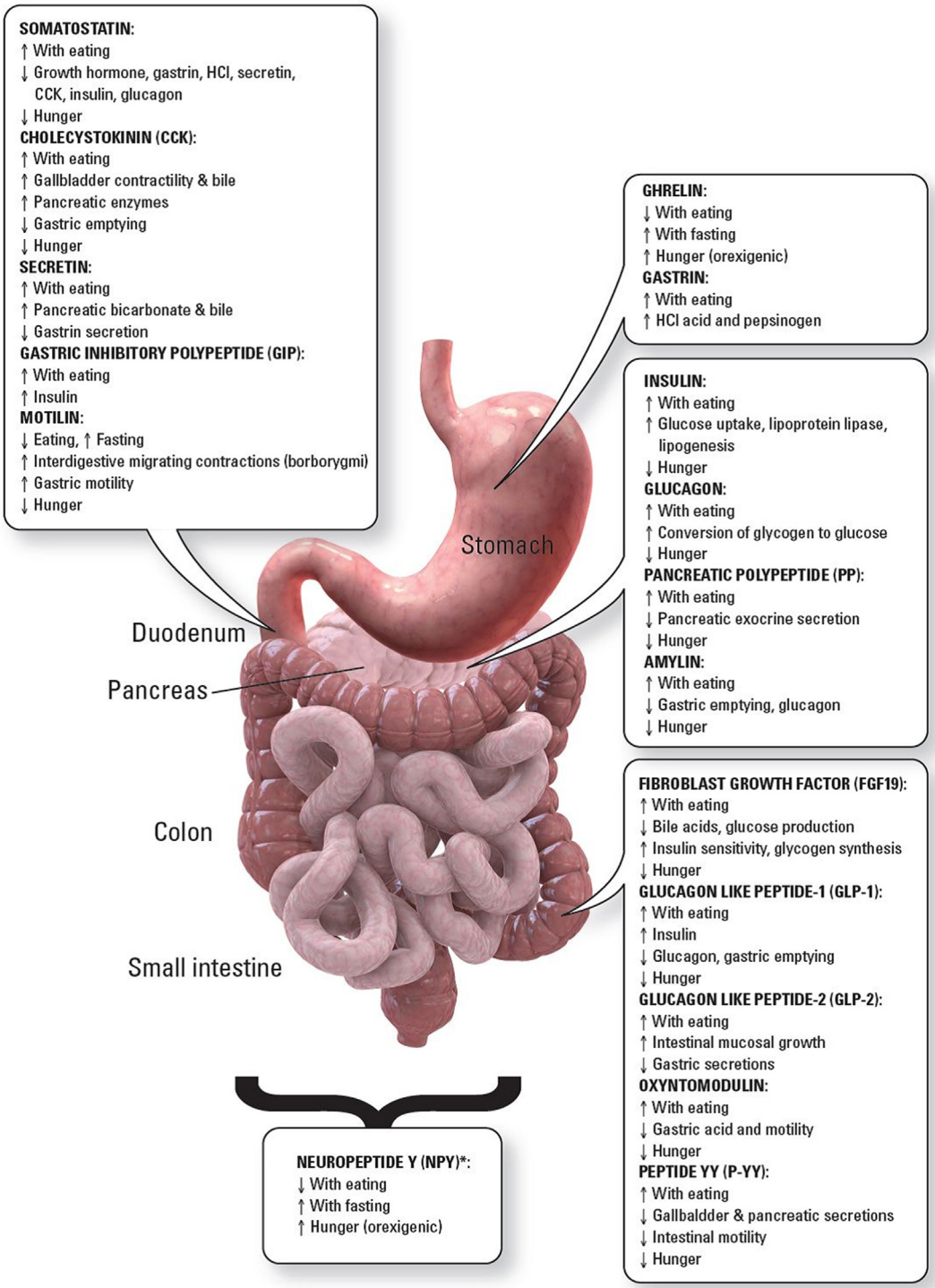

Fig. 1. Gastrointestinal hormones help regulate caloric balance, food digestion, and nutrient utilization. After fasting and before eating, gastrointestinal hormones may increase hunger (e.g., ghrelin and neuropeptide Y). After eating, gastrointestinal hormones may (1) decrease hunger/promote satiety (e.g., somatostatin, cholecystokinin, motilin, insulin, glucagon, pancreatic polypeptide, amylin, fibroblast grown factor 19, glucagon like peptide-1, oxyntomodulin, and peptide YY); (2) help manage digestion through slowing gastric motility/emptying (e.g., cholecystokinin, amylin, glucagon like peptide-1, oxyntomodulin, and peptide YY) (3) stimulate the release of digestive enzymes (e.g., gastrin, cholecystokinin, secretin); (4) have counter-regulatory functions in impairing digestive enzyme release (e.g., somatostatin, secretin, pancreatic polypeptide, glucagon like peptide 2, oxyntomodulin, peptide YY); and/or may assist with postabsorptive systemic nutrient management after digestion (e.g., somatostatin, insulin, glucagon, fibroblast growth factor 19).
*Neuropeptide Y (NPY) is a member of the pancreatic polypeptide-peptide family, expressed at all levels of the gut. NPY is also produced in the brain, and is the most abundant neuropeptide in the brain, involved with appetite and pain sensation functions.

Table 1
Bariatric procedure effects on hormones affecting nutrient metabolism and lipid blood levels.

Gut hormones (most are peptide hormones)	Description	Lipid effects of bariatric procedures	References
Stomach			
Ghrelin	Stomach ghrelin (name is derived from growth hormone releasing peptide) stimulates pituitary growth hormone release, increases gastric motility, and acts on the feeding center of the hypothalamus to stimulate hunger. Ghrelin may have direct cardiovascular effects, such as coronary artery constriction, and yet protective effects against myocardial ischemia, decreased peripheral vascular resistance with vasodilation, increased cardiac output, decreased blood pressure, increased cardiac contractility, increased exercise capacity, and inhibition of apoptosis of endothelial cells and cardiomyocytes. Conversely, stimulation of eating behavior with ghrelin may increase cardiovascular disease risk factors such as obesity, adiposopathy, and increased risk for insulin resistance, hyperglycemia, nonalcoholic fatty liver disease, high blood pressure, and mixed dyslipidemia. Ghrelin may be influenced by the gut microbiome (see Part 1 of this Scientific Statement) and is among the few gut hormones that is orexigenic. As opposed to most other gut hormones, ghrelin increases with fasting and decreases with eating.	Bariatric surgery has variable effects on ghrelin, depending on the type of surgery, timing of postoperative ghrelin measurements, and the size of the remaining remnant gastric pouch. In general, gastric bypass and sleeve gastrectomy decrease ghrelin levels, which may decrease food intake, improve insulin sensitivity, reduce the risk of nonalcoholic fatty liver disease, and potentially improve dyslipidemia.	[3,11–17]
Gastrin	Gastrin is structurally similar to cholecystokinin and stimulates stomach exocrine cells to secrete hydrochloric acid and pepsinogen (which is activated to pepsin by the hydrochloric acid). Pepsin assists with protein digestion. Gastrin increases with eating.	Bariatric surgery has variable effect on postoperative gastrin levels, depending on the type of surgery. Sleeve gastrectomy appears to most consistently increase gastrin levels. It is unclear that alterations in gastrin secretion affect lipid levels.	[12,13,15]
Pancreas			
Insulin	Insulin binds to insulin receptors of tissues such as adipose tissue and skeletal muscle, stimulates cellular glucose uptake, reduces glucose blood levels, increases lipoprotein lipase activity, and increases lipogenesis. Insulin increases with eating and, when not associated with hypoglycemia, increased central nervous system insulin may promote satiety.	Bariatric procedures may improve postoperative β-cell function, insulin release, and insulin sensitivity, especially procedures such as gastric bypass and sleeve gastrectomy. Improvement in glucose metabolism via enhanced insulin sensitivity may improve mixed dyslipidemia.	[3,11,12,20]
Glucagon	Glucagon is produced by pancreatic α-cells and converts stored liver glycogen to glucose, thus raising glucose levels. Glucagon may increase adipose tissue lipolysis. *Glucagon increases with eating and may promote satiety.	Bariatric surgery (e.g., gastric bypass) may result in a transient rise in postoperative glucagon. To the extent that increased postoperative glucagon may promote satiety, this could conceivably help account for improved dyslipidemia with bariatric surgery.	[19,21–24]
Pancreatic polypeptide	Pancreatic polypeptide inhibits pancreatic exocrine secretion. It increases with eating and may promote satiety.	Bariatric surgery has variable reported effects on postoperative pancreatic polypeptide. To the extent that increased postoperative pancreatic polypeptide may promote satiety, this could conceivably help account for improved mixed dyslipidemia with bariatric surgery.	[12,23,25–27]
Amylin	Amylin is co-secreted with insulin from the pancreatic β-cells, delays gastric emptying, and inhibits glucagon release. Increased amylin levels are associated with hypertriglyceridemia. Amylin increases with eating and may promote satiety.	Bariatric surgery may decrease postoperative amylin levels, with gastric bypass more so than gastric banding. Although unclear that reducing amylin levels per se reduce triglyceride levels, weight reduction reduces both amylin and triglyceride levels.	[28–30]

Table 1
Continued.

Gut hormones (most are peptide hormones)	Description	Lipid effects of bariatric procedures	References
Duodenum			
Somatostatin	Somatostatin is produced in the pyloric antrum and duodenum and inhibits growth hormone secretion. Somatostatin also inhibits the release of gastrin and hydrochloric acid from the stomach, inhibits the release of secretin and cholecystokinin from the duodenum, inhibits insulin and glucagon from the pancreas, and decreases gut motility. Somatostatin may decrease hepatic bile excretion, which may affect lipid levels (see Part 1 of this Scientific Statement). Somatostatin increases with eating and may promote satiety.	Bariatric surgery may not change postoperative somatostatin levels; lipid levels are unlikely altered by this mechanism.	[12,18,19]
Cholecystokinin (CCK)	CCK stimulates the gallbladder to contract and force bile into the intestine, stimulates pancreatic digestive enzyme secretion, inhibits gastric acid secretion, and slows gastric emptying. CCK increases with eating and may promote satiety.	Although the data is inconsistent, bariatric surgery may increase postoperative CCK levels, especially after a meal stimulus. The potential effect of increased CCK on lipid levels is mixed.[†]	[12,13,15,31]
Secretin	Secretin stimulates pancreatic bicarbonate secretion to neutralize acidity of gastric contents, stimulates hepatic bile secretion, inhibits gastric secretion, and increases lipolysis in adipocytes. Secretin increases with eating.	The effect of bariatric surgery on postoperative secretin is unclear and is likely dependent on the type of bariatric surgery.	[12,32]
Gastric inhibitory peptide, also known as glucose-dependent insulinotropic peptide (GIP)	GIP is an incretin that increases pancreatic insulin secretion, increases lipoprotein lipase in adipose tissue, increases fatty acid uptake by adipocytes, inhibits gastric secretion, and delays intestinal motility. GIP increases with eating.	Preoperatively, GIP levels may be increased in patients with obesity and diabetes mellitus. To the extent that increased GIP increases insulin and lipoprotein lipase, and facilitates fatty acid uptake by adipocytes, then increased GIP would improve dyslipidemia. Although reports are variable, bariatric surgery (e.g., gastric bypass) may reduce GIP levels, which may reflect improvements in glucose and lipid metabolism by other mechanisms.	[12,33,34]
Motilin	Motilin stimulates gallbladder contraction, promotes enzyme secretion from the stomach and pancreas, and stimulates gastric motility. Motilin may increase adipocyte proliferation, differentiation, fatty acid storage, and lipogenesis. Motilin is released during fasting and after eating and may serve to clear the stomach an intestine from undigested material. Some reports suggest motilin may promote satiety.	Bariatric surgery (jejunoileal bypass) may increase postoperative basal and postprandial motilin secretion. Increased energy storage in adipocytes may improve mixed dyslipidemia.	[35–38]
Ileum and large intestine			
Fibroblast growth factor (FGF19)	FGF19 is expressed upon activation of farnesoid X receptors (FXR) by intestinal bile acids. FGF19 reduces the activity of cytochrome P7 A1 (CYP7 A1), the rate-limiting step of bile acid synthesis, and thus decreases hepatic bile acid production. FGF19 also increases insulin sensitivity, inhibits glucose production, stimulates hepatic glycogen synthesis, may increase fatty acid β-oxidation, and may decrease lipid blood levels. FGF19 increases with eating, and may promote satiety.	Bariatric surgery (e.g., gastric bypass) may alter postoperative bile acid metabolism, increase bile acid blood levels, and increase FGF19. In addition to the improvement in lipid levels with favorable bile acid metabolism (see Part 1 of this Scientific Statement), FGF19 mediated satiety may improve dyslipidemia.	[39–41]
Glucagon like peptide-1 (GLP-1)	Incretin GLP-1 is produced by L-cells located in the ileum and large intestine and stimulates pancreatic insulin secretion, inhibits pancreatic glucagon secretion, inhibits gastric secretion,	Bariatric surgery may increase postoperative GLP-1 activity, especially after a meal stimulus. GLP-1 agonists improve glucose metabolism, decrease secretion of apolipoprotein B48	[11,12,19,25,29,42]

Table 1
Continued.

Gut hormones (most are peptide hormones)	Description	Lipid effects of bariatric procedures	References
	and inhibits gastric emptying. GLP-1 may be influenced by the gut microbiome (see Part 1 of this Scientific Review). GPL-1 may also mediate secretion of apolipoprotein B48 chylomicron secretion from the intestine. GLP-1 increases after meals and may promote satiety.	chylomicron secretion from the intestine, and promote satiety, all of which may contribute to their reduction in low-density lipoprotein cholesterol and triglycerides; high-density lipoprotein cholesterol may not be significantly changed.	
Glucagon like peptide-2 (GLP-2)	Incretin GLP-2 is produced by L-cells and inhibits gastric secretion, promotes intestinal mucosal growth, and promotes tissue repair. GPL-2 analogues may therapeutically improve the dependence on parenteral nutrition or intravenous fluid among those with short bowl syndrome. GLP-2 enhances intestinal digestive and absorptive capacities, including increases in chylomicron release into the circulation. GLP-2 increases after meals.	Bariatric surgery (e.g., gastric bypass) may increase postoperative GLP-2 levels, especially after a meal stimulus. Although administration of GLP-2 may increase postprandial triglyceride-rich lipoproteins in the form of stored apoB-48 chylomicrons, this effect is transient and unlikely a long-term effect found with bariatric surgery. To the extent GLP-2 promotes satiety and facilitates weight loss, this would be expected to improve dyslipidemia.	[12,15,43–45]
Oxyntomodulin	Oxyntomodulin is produced by L-cells and inhibits gastric acid production, reduces gastric motility, and may improve glucose metabolism. Oxyntomodulin increases with eating and may promote satiety.	Bariatric surgery (e.g., gastric bypass) may increase postnutrient ingestion oxyntomodulin levels. Improved glucose metabolism and promotion of satiety may facilitate decrease triglyceride levels.	[12,46,47]
Peptide YY 3-36 (PYY)	PYY is produced by L-cells and inhibits gallbladder and pancreatic secretion and reduces gut motility. PYY may be influenced by the gut microbiome (see Part 1 of this Scientific Review). PYY may also reduce the expression of intestinal Niemann-Pick C1-Like-1 (NPC1 L1) resulting in reduced intestinal cell cholesterol absorption. PYY increases with eating, and may promote satiety.	Although the data are not always consistent, bariatric surgery (e.g., gastric bypass) may increase postoperative PYY, especially after a meal stimulus. PYY-mediated inhibition of intestinal cholesterol absorption would be expected to reduce cholesterol levels. This is similar to ezetimibe, which also inhibits cholesterol uptake through the NPC1 L1 intestinal receptor. Promotion of satiety would also be expected to improve dyslipidemia.	[11,12,15,25,29,48,49]
Throughout gastrointestinal tract			
Neuropeptide Y (NPY)	NPY is produced in the central and peripheral nervous system, including the sympathetic nerves of the gut (co-released with norepinephrine). NPY is involved with inflammatory processes, pain, emotion, mood, cognition, and stress resilience, as well as energy homeostasis and hunger. NPY may increase hepatic VLDL secretion from the liver. NPY may be influenced by the gut microbiome (see Part 1 of this Scientific Review). NPY is orexigenic and increases with fasting and decreases with eating.	Bariatric surgery may not change postoperative basal NPY levels, but gastric bypass may reduce postprandial NPY secretion. Reducing NPY activity, and thus diminishing VLDL secretion and NPY's orexigenic effects, would be expected to improve mixed dyslipidemia.	[33,50–53]

VLDL = very low density lipoprotein.
*Although not confirmed, some older reports suggest glucagon may modestly improve lipid levels.
†An increase in bile secretion may improve cholesterol and triglyceride absorption from the intestine, which may promote hyperlipidemia. Decreased caloric intake from increased satiety may decrease cholesterol and triglyceride intake, thus decreasing hyperlipidemia.

Afterward, free fatty acids undergo activation by CoA, which is an esterification process required for fatty acid oxidation, synthesis of triglycerides, or attachment to proteins. The 3-carbon glycerol for which the 3 activated fatty acids are attached in forming triglycerides originates from glucose or pyruvate. Thus, adipocytes must have access to both free fatty acids and glucose to store fatty acids as triglycerides. Through a number of enzymatic steps involving the formation of lysophatidic acid (one fatty acid), and then phosphatidic acid and diacylglycerol (both 2 fatty acids), glycerol-3-phosphate may ultimately be esterified with 3 fatty acids (often mixed in size) through the terminal enzymatic step involving diacylglycerol acyltransferase (DGAT). In addition to hormones (similar to hormone-sensitive lipase), lipoprotein lipase activity may also be affected by apolipoproteins and drugs. Although insulin may decrease hormone-sensitive lipase (limiting fatty acid release from

adipocytes), insulin increases lipoprotein lipase activity, which reduces triglyceride blood levels. Apolipoprotein C-III (ApoC-III) is a small protein that resides on triglyceride-rich VLDL and chylomicron particles that inhibits lipoprotein lipase, impairs hepatic uptake of triglyceride-rich lipoproteins (e.g., lipoprotein remnants), contributes to insulin resistance, and generally promotes elevated triglyceride levels. Fibrates and omega-3 fatty acids are lipid-altering pharmacotherapies that reduce ApoC-III levels, increase lipoprotein lipase activity and thus lower triglyceride blood levels.

The hormone effects on hormone-sensitive lipase and lipoprotein lipase affect circulating free fatty acid levels. After meals, circulating free fatty acids are dramatically decreased (by 70%–90%), substantially as a result of increased insulin levels, which upregulate lipoprotein lipase and downregulate hormone-sensitive lipase, reducing triglyceride blood levels, increasing transport of fatty acids into fat cells, and "trapping" fatty acids in the form of intracellular triglycerides (because of reduced intracellular triglyceride lipase activity). During fasting, decreased insulin levels downregulate lipoprotein lipase and upregulate hormone-sensitive lipase, and increase the release of free fatty acids from adipocytes into the circulation. These circulating free fatty acids may undergo β-oxidation by muscle for energy or undergo hepatic β-oxidation, ketogenesis, lipogenesis, and gluconeogenesis. Prolonged fasting for longer than 7 days may markedly increase circulating free fatty acids, resulting in hepatosteatosis, ketosis, and insulin resistance and potentially a rise in triglyceride blood levels.

Especially if adipocytes have adiposopathic impairment of adipogenesis and function, then during times of positive caloric balance, free fatty acids not stored in adipocytes and may be shunted to other body tissues, such as the liver, muscle, and pancreas. This may result in "lipotoxicity," which is the dysfunction of body organs promoted by deposition of excessive free fatty acids and their products (e.g., ceramides and diacylglycerols). Lipotoxicity may result in hepatic and muscle insulin resistance, potential insulinopenia from the pancreas, and dysfunction of other body organs (e.g., the heart, vasculature, kidney). Patients with type 2 diabetes often have increased circulating fasting and postprandial free fatty acids compared with those without type 2 diabetes, and also often have increased insulin resistance and decreased pancreatic insulin release relative to glucose levels. In summary, elevated circulating free fatty acids may contribute to "lipotoxicity." The levels of free fatty acids in the circulation can be attributable to: (1) postprandial or fasting state; (2) adipose tissue storage capacity; and (3) the degree by which other body organs either store free fatty acids as triglycerides or metabolize free fatty acids. The processes involved in intestinal fat metabolism are dependent on intestinal digestion and gut hormones. Table 1 describes bariatric procedure effects on gut hormones important for fat and lipid digestion, which may influence lipid levels [3,11–53].

Intestinal carbohydrate metabolism

Monosaccharides can be directly absorbed through the mouth mucosa (e.g., therapeutic use of oral glucose agents to treat hypoglycemia), whereas consumed plant starches and animal glycogen must undergo digestion from chewing and salivary gland amylase, which begins to hydrolyze these complex carbohydrates to more simple sugars. Once in the small intestine, chyme (the acidic gastric juices and partially digested food) promotes release of cholecystokinin by small intestine L-cells, causing the release of bile from the gallbladder, as well as digestive juices from the pancreas, which include: (1) lipase, cholesteryl esterase, and phospholipase for fat digestion; (2) trypsin, chymotrypsin, and carboxypolypeptidase for protein digestion; and (3) amylase, which further catalyzes the hydrolysis of complex carbohydrates (e.g., starches and glycogen, not cellulose) to more simple sugars (Fig. 1; Table 1) [3,11–53]. Afterward, monosaccharides (e.g., glucose, fructose, galactose) are mostly absorbed across the brush border of the small intestine by transporters, such as facilitative passive hexose glucose transporters (e.g., GLUT-2, GLUT-5, etc.) or active sodium-coupled glucose cotransporters (e.g., SGLT-1, etc.) [56]. The major circulatory hexose transporter found in adipocytes and muscle is GLUT-4, which is regulated by insulin. Once delivered to the liver or muscle, fructose and galactose are converted to glucose. Once glucose is phosphorylated, it may interact with uridine triphosphate to form uridine diphosphate glucose, which allows for linkage to other glucose and, ultimately, glycogen formation. Lipogenesis is limited in muscle. In the liver, if glycogen stores are replete, then an increased dietary consumption of carbohydrates may increase circulating insulin and glucose and, through SREBP-1–mediated increase in lipogenic gene expression, increase fat storage in the liver. In adipocytes, the increase in circulating insulin and glucose from consumption of carbohydrates may promote peroxisome proliferator activated receptor γ–mediated lipogenic gene expression. Although not clear that simple sugars differ in their potential adverse health effects when evaluated in the manner typically consumed, and at typical amounts in the human diet [57], fructose (such as from high-fructose corn syrup) is often described as especially promoting fatty liver, obesity, and insulin resistance [58]. The processes involved in carbohydrate metabolism are dependent on intestinal digestion and gut hormones. Table 1 describes bariatric procedures' effects on gut hormones important for carbohydrate digestion, which may influence lipid levels [3,11–53].

Intestinal protein metabolism

Proteins are metabolized in the stomach by gastric acid (hydrochloric acid, potassium chloride, and sodium chloride) secreted by stomach parietal cells, which breaks down

proteins into amino acids. Other stomach epithelial lining cells produce gastric pepsin (most active at low pH), which breaks down collagen, the main structural protein found in animal connective tissue. Once in the small intestine, cholecystokinin-mediated release of trypsin, chymotrypsin, and carboxypolypeptidase (Fig. 1; Table 1) [3,11–53] from the pancreas continues to hydrolyze proteins into amino acids, which are then absorbed into circulation (Fig. 1; Table 1) [3,11–53]. Once delivered to the liver, surplus amino acids undergo deaminization and are converted into glucose via the alanine cycle. Nitrogen from the amine group of amino acids is converted to urea (e.g., urea cycle), which is excreted by the kidney. The carbon components of amino acids may also be converted to keto acids, giving rise to acetyl-CoA and generation of fatty acids for lipogenesis. The processes involved in intestinal protein metabolism are dependent on intestinal digestion and gut hormones. Table 1 describes bariatric procedures' effects on gut hormones important for protein digestion, which may influence lipid levels [3,11–53].

Bariatric procedures and nonlipid atherosclerotic cardiovascular disease risk factors

Patients with obesity are at increased risk for cardiovascular disease [59]. Improvement in dyslipidemia is an important health benefit of bariatric procedures, helping to account for a reduction in CVD risk. However, bariatric procedures reduce multiple CVD risk factors [60]. Table 2 lists a number of CVD disorders caused by adiposopathy [61]. Table 3 describes the potential effects of bariatric procedures on atherosclerotic cardiovascular disease (ASCVD) risk factors, as well as adiposopathic markers that may contribute to metabolic disease, most of which are ASCVD risk factors [62–117].

Bariatric procedures and dyslipidemia

Lipids and atherosclerosis

An increase in atherogenic lipoprotein particle number is a root cause of atherosclerosis [118,119]. Lipoprotein concentration can be measured directly [120] or via the surrogate measure of apolipoprotein B (apoB), wherein 1 molecule of apoB resides on every atherogenic lipoprotein [120,121]. ApoB is thus a measure of the concentration of cholesterol-containing atherogenic lipoproteins such as LDL, VLDL, IDL, and VLDL remnants. The cholesterol carried by these atherogenic lipoproteins is termed *atherogenic cholesterol*, even as it is recognized that apoB–containing and cholesterol-containing lipoproteins themselves more precisely promote atherosclerosis [118,119].

Multiple epidemiologic studies have long supported the "cholesterol hypothesis." An increase in atherogenic cholesterol increases ASCVD risk, and a decrease in atherogenic cholesterol reduces ASCVD risk [118]. The 2013 National Lipid Association Consensus Statement on the lipid effects of obesity noted that adipocytes and adipose tissue store the greatest amount of body lipids, including triglycerides and free cholesterol [3]. This Consensus Statement also acknowledged that adipocytes and adipose tissue have active endocrine and immune functions, whose disruption results in adiposopathy. Among the cellular findings of adiposopathy include adipocyte hypertrophy (potentially resulting in dysfunction of intracellular organelles such as mitochondria and endoplasmic reticula), growth of adipose tissue beyond its vascular supply (potentially contributing to adipocyte and adipose tissue hypoxia), increased number of adipose tissue immune cells (increasing the potential for proinflammatory responses, such as increased tumor necrosis factor, interleukin-6, and C-reactive protein), and ectopic fat deposition in

Table 2
Adverse cardiovascular health consequences of adiposopathy, which may be improved with weight loss, such as through bariatric procedures [61]*

Increased adiposity (excessive fat mass)
Sleep apnea
Thromboembolic events
Increased blood volume
Increased cardiac output
Atrial enlargement
Ventricular dilation
Electrocardiogram abnormalities: increased heart rate, increased PR interval, increased QRS interval, decreased QRS voltage (although sometimes increased), increased QTc interval, abnormal signal-averaged electrocardiogram late potentials, ST–T-wave abnormalities, left-axis deviation, criteria for left ventricular hypertrophy, flattening of the T-waves (inferolateral leads), left atrial abnormalities, and false positive criteria for inferior myocardial infarction
Adiposopathy (adipose tissue dysfunction)
Type 2 diabetes
High blood pressure
Dyslipidemia
Metabolic syndrome
Atherosclerosis
Cardiomyopathy ("fatty heart")

*Some cardiovascular diseases may be due to both worsening fat function and excessive fat mass.

Table 3
Potential effects of bariatric procedures on illustrative nonlipid atherosclerotic cardiovascular disease (ASCVD) risk factors and adiposopathic markers that may contribute to metabolic disease, most of which are ASCVD risk factors*

ASCVD Risk factor	Effect of bariatric procedures	References
Glucose		[62]
Glucose levels	↓	[63,64]
Diabetes mellitus remission	↑	[63,65–68]
Blood pressure		[69–75]
Systolic blood pressure	↓	[63,76]
Diastolic blood pressure	↓	[63,76]
Hypertension remission	↑	[63,77]
Thrombotic factors		
Fibrinogen	↓	[78,79]
Stroke	↓	[80]
Homocysteine	–↓	[81,82]
Plasminogen activator inhibitor-1	↓	[79,83]
Kidney function (among patients with chronic kidney disease)		
Albuminuria	↓	[84–88]
Proteinuria	↓	[84]
Uric acid	↓	[89]
Glomerulofiltration rate	↑	[84]
Adipose tissue and adipocyte factors		
Waist circumference	↓	[90–92]
Leptin	↓	[93–95]
Adiponectin	↑	[93–96]
Inflammatory markers		[97]
C-reactive protein	↓	[83,85,93,94,98–104]
Interleukin-6	↓	[96,97,99,100,105]
Tumor necrosis factor	– ↓	[93,103–106]
Lipoprotein phospholipase a2	–↓	[107,108]
Oxidized low-density lipoprotein	↓	[107]
Oxidative stress	↓	[109]
Liver		
Transaminase elevation	↓	[110]
Fatty liver by imaging	↓	[110]
Vascular markers		
Coronary calcium	↓	[111]
Endothelial function	↑ –	[94,112–116]
Carotid intima-medial thickness	↓	[115,116]
Ankle brachial index / pulse wave Velocity	Improved	[117]

*The effects of all bariatric procedures on these ASCVD risk parameters were not reported for all bariatric procedures.

nonadipose body organs (e.g., liver and muscle). If peripheral subcutaneous adipose tissue storage is limited, then positive caloric balance may also result in "energy overflow" to other fat depots, such as visceral, pericardial, perivascular, and other periorgan fat. Thus, during positive caloric balance, the limitation in energy (i.e., fat) storage in peripheral subcutaneous tissue combined with an increase in fat deposition in other fat depots helps explain why visceral adiposity might be considered a surrogate marker for global fat dysfunction and why central obesity is a clinical marker of adiposopathy [7].

Adiposopathy ("adipose-opathy," or "sick fat") is defined as pathologic adipose tissue anatomic and functional disturbances promoted by positive caloric balance in genetically and environmentally susceptible individuals that results in adverse endocrine and immune responses, which in turn may promote metabolic diseases (e.g., dyslipemia, hyperglycemia, high blood pressure, etc.) and cardiovascular disease [61]. Adiposopathic mixed dyslipidemia is often found in patient with overweight or obesity and is characterized by increased levels of triglyceride-rich lipoproteins, reduced HDL cholesterol, as well as increased LDL particle number and increased proportion of smaller, denser LDL particles [3,119]. Examples of adipocyte and adipose tissue endocrine factors affiliated with adiposopathic dyslipidemia include: (1) adverse disruption of lipid metabolism proteins, enzymes, and hormones; (2) pathogenic patterns of lipids and apolipoproteins; (3) abnormalities of lipid transfer proteins and biologic transporters; and (4) anomalies of cellular receptors [3]. Adipocyte and adipose tissue immune factors may also contribute to adiposopathic dyslipidemia via the imbalance between the proinflammatory and anti-inflammatory factors secreted by adipocytes, as well as by the macrophage-enriched surrounding adipose tissue stroma [3].

Appropriate nutritional intervention, increased physical activity, and weight management pharmacotherapy can

improve adipocyte and adipose tissue function in patients who are overweight or obese and may improve many of the components of adiposopathic mixed dyslipidemia [3]. Another intervention that may improve both the weight and the metabolic health of patients with overweight or obesity is bariatric surgery. In a 2009 consensus manuscript, bariatric surgery was determined to be a potential treatment for adiposopathy. Bariatric surgery improves adipocyte and adipose tissue endocrine and immune functions, improves adipocyte and adipose tissue secretory patterns associated with improved metabolic health, reduces circulating free fatty acids (although free fatty acids may increase during the initial stages of postoperative weight loss), and reduces visceral adiposity, which, as noted before, is a marker of global fat dysfunction and suggestive of increased risk for cardiovascular disease [122].

Bariatric procedures

The methods by which bariatric procedures are performed and the frequency of the bariatric procedures are constantly evolving. Originally performed in 1892, the Roux-en-Y surgery was originally performed to "bypass" the stomach to treat antral or pyloric obstruction [122]. Since then, a number of bariatric surgical procedures have evolved, with an increasing adoption of a minimally invasive laparoscopic approach. At the time of this writing, the most common bariatric surgical procedures are Roux-en-Y gastric bypass and sleeve gastrectomy. Other less common bariatric procedures include adjustable gastric banding and biliopancreatic diversion with duodenal switch (vertical banded gastroplasty is no longer performed). In the past, these bariatric surgical procedures were often categorized as "restrictive" (e.g., sleeve gastrectomy, laparoscopic gastric banding, and vertical banded gastroplasty) or "malabsorptive" (e.g., Roux-en-Y gastric bypass and biliopancreatic diversion bypass). However, such distinctions are somewhat artificial in that the weight loss effectiveness of "restrictive" bariatric procedures may be somewhat independent of the degree by which they restrict food intake and may be more related to neurohormonal feedback to appetite centers. Similarly, some of the effectiveness of the Roux-en-Y gastric bypass may be related to limitations in food storage via bypassing the stomach, which would otherwise have the potential for greater food-holding capacity. Finally, although laparoscopic gastric banding (sometimes considered "restrictive") may result in less weight loss than other bariatric procedures, and although biliopancreatic diversion bypass (sometimes considered "malabsorptive") may result in more weight loss than other bariatric procedures, it is unclear that the "restrictive" versus "malabsorptive" labeling alone is predictive of weight loss or health outcomes. Having said this, malabsorptive bariatric procedures generally have greater effects on gut hormones (Table 1) [3,11–53] than gastric banding [29,123].

"Malabsorptive" surgical procedures are often described to represent "metabolic surgeries," in that such procedures may alter gastrointestinal hormonal secretions and favorably influence intestinal bile acids, microbiota, and intestinal gluconeogenesis, which all may contribute to improvement in metabolic diseases, possibly independent of weight loss [65,124]. However, laparoscopic Roux-en-Y gastric bypass (sometimes considered "malabsorptive") and sleeve gastrectomy (sometimes considered "restrictive") may have similar degrees of weight loss and improved metabolic health outcomes (e.g., dyslipidemia, diabetes mellitus, high blood pressure) [125,126]. Given the similarities in weight loss and metabolic outcomes with the "malabsorptive" laparoscopic Roux-en-Y gastric bypass and the "restrictive" sleeve gastrectomy bariatric procedures, all common bariatric procedures might best be considered "metabolic" surgical procedures. That is because the most consistent and unifying aspect of all of these common bariatric procedures is the reduction in body fat, which improves adipocyte and adipose tissue function, and which in turn improves metabolic disease [122]. Thus, the choice of the preferred bariatric procedures for metabolic diseases (including dyslipidemic patients with overweight or obesity) is best determined by the anticipated risks and benefits, expertise of the surgeon and affiliated facility, as well individual characteristics and preferences of the patient. Another consideration is comparative health metabolic outcomes (e.g., dyslipidemia, type 2 diabetes mellitus, hypertension) wherein gastric bypass ("malabsorptive") may have improved long-term metabolic outcomes compared with gastric banding ("restrictive") [63]. What may be less important in the bariatric procedure selection is the somewhat artificial and perhaps unhelpful "restrictive" versus "malabsorptive" label, at least with respect to comparisons of the expected weight loss and metabolic effects of laparoscopic Roux-en-Y gastric bypass versus sleeve gastrectomy.

Bariatric procedures and lipid effects

Table 4 describes the effects of various bariatric procedures on lipid parameters [81,107,127–149]. Some observations include the following:

1. The greater the fat mass loss, the greater the improvement in dyslipidemia. According to the 2014 Cochrane Collaboration update on surgery for weight loss in adults [125], compared with nonsurgical interventions, bariatric surgery results in greater improvement in weight loss adverse health consequences, regardless of the type of procedures used. In general, weight loss is similar between Roux-en-Y gastric bypass and sleeve gastrectomy, with both promoting greater weight loss than adjustable gastric banding. For patients with very high

Table 4
Potential effects of bariatric procedures on illustrative lipid parameters

Lipid parameters	Effect of bariatric procedure	References
Adjustable gastric banding		
Low-density lipoprotein cholesterol	↓	[130]
Non–high-density lipoprotein cholesterol	–	[131]
Apolipoprotein B	–	[132]
Lipoprotein particle number	↓ –	[133,134]
Total cholesterol	↓	[130,135]
Triglycerides	↓	[133,135]
High-density lipoprotein cholesterol	↑	[133,135,136]
Lipoprotein remnants	Not reported	
Lipoprotein (a)	–	[81]
Low-density lipoprotein particle size	–	[133]
Sleeve gastrectomy		
Low-density lipoprotein cholesterol	↓	[137,138]
Non–high-density lipoprotein cholesterol	↓	[139]
Apolipoprotein B	↓	[140]
Lipoprotein particle number	↓	[134]
Total cholesterol	↓	[138,139]
Triglycerides	↓	[137–139]
High-density lipoprotein cholesterol	↑	[137–139]
Lipoprotein remnants	↓	[129]
Lipoprotein (a)	–	[141]
Low-density lipoprotein particle size	–	[142]
Gastric bypass		
Low-density lipoprotein cholesterol	↓	[127,130,138,143,144]
Non–high-density lipoprotein cholesterol	↓	[145]
Apolipoprotein B	↓	[107]
Lipoprotein particle number	↓	[134]
Total cholesterol	↓	[127,130,138,143]
Triglycerides	↓	[127,138,143,144]
High-density lipoprotein cholesterol	↑	[127,128,136,138,144,146]
Lipoprotein remnants	↓	[128]
Lipoprotein (a)	–	[143]
Low-density lipoprotein particle size	↑	[147]
Biliopancreatic diversion/duodenal switch		
Low-density lipoprotein cholesterol	↓	[131,148,149]
Non–high-density lipoprotein cholesterol	↓	[131]
Apolipoprotein B	↓	[149]
Lipoprotein particle number	Not reported	
Total cholesterol	↓	[149]
Triglycerides	↓	[149]
High-density lipoprotein cholesterol	↑	[131,136]
Lipoprotein remnants	Not reported	
Lipoprotein (a)	Not reported	
Low-density lipoprotein particle size	Not reported	

body mass index, biliopancreatic diversion with or without duodenal switch may result in greater weight loss than Roux-en-Y gastric bypass. Many of the reports referenced in Table 4 [81,107,127–149] are consistent with the notion that the greater the fat mass loss, the greater the improvement in lipid (and other metabolic) parameters [150], as often occurs with the more "malabsorptive" procedures [151,152]. Table 4 [81,107,127–149] describes the major lipid parameters most often reported as improved and includes reductions in LDL cholesterol, total cholesterol, and triglyceride levels, as well as (after 6 mo or so), increases in HDL cholesterol.

2. Data regarding the lipid effects of biliopancreatic diversion/duodenal switch are less reported than with laparoscopic gastric banding, Roux-en-Y gastric bypass, and sleeve gastrectomy, probably because it is a less common bariatric procedure.
3. Bariatric procedures allow for a decrease in the use of drugs for treatment of dyslipidemia [127,153], as well as a decrease in drugs used for treatment of diabetes mellitus and blood pressure, compared with medical therapy for obesity [154,155]. Thus, not only are bariatric surgeries superior to medical management in improving metabolic parameters among patients with obesity, but bariatric procedures often allow for less

polypharmacy postoperatively. This may allow for both improved lipid levels and reduced lipid-altering drug therapies [156].

4. HDL cholesterol may decrease during active weight loss (particularly the first 6 mo after bariatric surgery) and then may ultimately increase above baseline. The potential for an initial reduction in HDL cholesterol levels during active weight loss is a well-known phenomenon in clinical lipidology, occurring not only with bariatric procedures, but also some weight management pharmacotherapies, as well as nutritional weight loss—especially with fat-restricted nutritional intervention [3]. As per Part 1 of this Scientific Statement, human trials suggest that within the first 6 months during rapid weight loss with bariatric surgery, both HDL and apoE decrease. The initial drop in HDL cholesterol levels may reflect the gradual qualitative switch of HDL from apoE-containing to more functional apoAI-containing HDL particles [128,157,158].

One of the primary, if not the primary, lipid treatment target is non-HDL cholesterol, which includes the cholesterol carried by all atherogenic lipoproteins (e.g., the cholesterol carried by low-density lipoproteins, intermediate-density lipoproteins, very low density lipoproteins, VLDL remnants, chylomicrons, chylomicron remnants, and lipoprotein [a]) [118]. Non-HDL cholesterol is a calculation of total cholesterol minus the cholesterol carried by HDL particles (i.e., total cholesterol – HDL cholesterol). Likely because of its inclusive nature, non-HDL cholesterol is a better predictor of ASCVD risk than LDL cholesterol. Furthermore, changes in non-HDL cholesterol with dyslipidemia treatment are more strongly associated with reduced ASCVD risk than with on-treatment LDL cholesterol levels [119]. Yet despite its primary importance regarding diagnosis and treatment of dyslipidemia, non-HDL cholesterol is rarely reported in bariatric procedure clinical trials.

Similarly, an integral contributor to atherosclerosis is incorporation of atherogenic lipoproteins within the subendothelia, which promotes the inflammatory process potentially leading to ASCVD events (see Part 1 of this Scientific Statement). Given that 1 molecule of apoB resides on every atherogenic lipoprotein, apoB can be considered a surrogate for atherogenic lipoprotein particles. Diagnostically, whenever discordance exists between LDL cholesterol and either LDL particles or apoB, the latter 2 lipid parameter are superior in predicting ASCVD risk [119]. That is why apoB is sometimes considered a treatment target, with assigned treatment goals, by various international lipid guidelines [118,159,160]. Despite the central role of apoB and LDL particle numbers to atherosclerosis, these parameters are rarely reported in bariatric procedure clinical trials.

Yet another lipid parameter with scarce reporting is remnant lipoproteins. Increased triglyceride-rich lipoproteins are potentially transformed into lipoprotein remnants. Remnant particles may become incorporated into arterial subendothelia. Although remnant lipoproteins are much larger than LDL, and thus may have less potential to cross the endothelium, each remnant particle contains about 40 times more cholesterol compared with low-density lipoproteins. Thus, remnant lipoproteins are important contributors to atherosclerosis, and postprandial dyslipidemia is an important ASCVD risk factor [161,162]. Some literature supports that bariatric surgery improves both fasting and postprandial lipid levels, possibly because of impaired intestinal cholesterol absorption and improved insulin sensitivity, which might enhance postprandial clearance of triglyceride-rich lipoproteins [129,163,164]. However, given the high prevalence of hypertriglycemia in the population, the importance of remnant lipoproteins in the process of atherosclerosis, and the potential of bariatric procedures to improve clearance of triglyceride-rich lipoproteins and remnant lipoproteins, the amount of data regarding the effects of bariatric procedures on remnant lipoproteins could be more robust.

Finally, 2 other lipid parameters scarcely reported in trials of bariatric procedures include lipoprotein a (Lp[a]) and LDL particle size. Lp(a) is a lipoprotein similar to LDL and consists of an LDL molecule attached to a second protein, apo (a). Apo (a) has a structure similar to plasminogen. Although elevated Lp(a) is a risk factor for ASCVD, nutritional intervention or increased physical activity is not known to decrease its levels. Therefore, it is not surprising that on the rare instances Lp(a) was reported in bariatric procedure clinical trials, Lp(a) levels were not changed. The other lipid parameter scarcely reported is LDL particle size. Presumably, the smaller the LDL particle size (as often occurs in patients with adiposopathy, glucose intolerance, diabetes mellitus, and metabolic syndrome), the greater the potential to enter the arterial subendothelial wall. Furthermore, smaller LDL particles may have less affinity to LDL receptors, increasing their persistence in the circulation and exposure to the arterial endothelia. Smaller LDL particles are more easily oxidized upon interactions with subendothelial macrophages. However, although lipoprotein particle size may have diagnostic value, little evidence supports lipoprotein particle size as a treatment target or a clinically useful postintervention metric [119,120,165].

Bariatric procedures and atherosclerotic cardiovascular disease

Historical importance of intestinal procedures in validating the cholesterol hypothesis: Program on Surgical Control of the Hyperlipidemias (POSCH)

At least since the 1960s, intestinal surgery (i.e., ileal bypass) was employed as a way to reduce hyperlipidemia [166]. One of the first classic clinical trials to test the "cholesterol hypothesis" was the Program on Surgical

Control of the Hyperlipidemias (POSCH), which was a randomized, secondary intervention trial among patients with prior myocardial infarction, evaluating the combination of nutritional intervention and partial ileal bypass (PIB) [167]. In this study of 838 participants, an interim analysis revealed that 396 (196 control and 200 surgical patients) had complete 5-year lipoprotein results [168]. Compared with control patients, the PIB group had a 24% reduction in total cholesterol and a 38% reduction in LDL cholesterol. Also compared with the control group, although triglyceride and VLDL cholesterol levels were higher, the PIB group had significantly lower apolipoprotein B-100 levels (reflecting an overall reduction of atherogenic lipoprotein particle number), as well as consistently higher HDL cholesterol and apolipoprotein A-I and HDL-2 levels. It was noted these lipoprotein changes were greater than reported from previous trials of dietary or pharmacologic intervention, which at the time included clinical trial results of bile acid resins [169]. Based on these lipoprotein effects of this intestinal surgery, the hypothesized predictive outcome was that PIB would demonstrate a reduction in ASCVD morbidity and mortality. After a mean follow-up of 9.7 years, the PIB group had a statistically significant mean weight loss of 5.3 kg (weight in the control group was not reported) [170]. Compared with the control group, PIB was found to produce sustained improvement in lipid levels, as well as a statistically significant 35% reduction in the combined endpoints of death as a result of coronary heart disease and confirmed nonfatal myocardial infarction, as well as a statistically significant reduction in coronary artery bypass grafting and reduction in angiographic atherosclerotic lesion progression. PIB also resulted in a reduction in overall mortality (estimated 149 deaths per 1000 in the control group versus 116 per 1000 in the PIB group), although this did not achieve statistical significance. Overall, this sentinel trial of an intestinal surgical procedure provided "strong evidence supporting the beneficial effects of lipid modification in the reduction of atherosclerosis progression" [170].

Bariatric procedures, cardiovascular disease risk factors, cardiovascular disease outcomes, and overall mortality

Regarding cardiovascular disease risk factors, current bariatric surgical procedures for the purpose of weight loss have shown a consistent reduction in cardiovascular risk factors. Most studies of bariatric procedures report improvement in lipid levels (Table 4) [81,107,127–149], as well as improvement in glucose levels, blood pressure, endothelial function, C-reactive protein, and ASCVD risk scores, such as the Framingham risk score [60]. In a systematic review of cardiovascular risk factors [171], bariatric surgery improved hyperlipidemia in 65% of patients, as well as improved diabetes mellitus in 73% and hypertension in 63% of patients. Echocardiographic data after bariatric surgery indicated significant improvements in left ventricular mass and function [171].

Regarding cardiovascular events, in a meta-analysis of clinical trials comparing bariatric surgery versus nonsurgical treatment, bariatric surgery patients had a statistically significant reduction in myocardial infarction (odds ratio = .54), stroke (odds ratio = .49), and composite ASDVD events (odds ratio = .54) and a 50% reduction in overall mortality [80].

Regarding deaths, the Swedish Obese Patients (SOS) study was the first large-scale, long-term, prospective, controlled trial to report the effects of bariatric surgery on the incidence of cardiovascular disease and overall mortality, as well as diabetes mellitus and cancer [172]. The SOS study evaluated 2010 patients with obesity who underwent bariatric surgery (gastric bypass [13%], banding [19%], and vertical banded gastroplasty [68%]), and compared the health outcomes to 2037 contemporaneously matched obese control patients receiving usual care. The age of participants was 37–60 years and body mass index (BMI) was $\geq$34 kg/m^2 in men and $\geq$38 kg/m^2 in women. Follow-up periods varied from 10 to 20 years. The mean changes in weight after 2, 10, 15, and 20 years were –23%, –17%, –16%, and –18% in the surgery group and 0%, 1%, –1%, and –1% in the control group, respectively. Compared with usual care, bariatric surgery produced a reduction in overall mortality (primary endpoint) and myocardial infarction, as well as decreased diabetes mellitus, stroke, and decreased cancer in women. In a 2- and 10-year follow-up publication, LDL cholesterol, non-HDL, apolipoprotein B, and lipoprotein particle number were not reported. However, although total cholesterol did not statistically change at 10 years, bariatric surgery did produce significant decreases in triglyceride and significant increases in HDL cholesterol levels [3,173].

Postbariatric deficiencies of vitamins, minerals, and trace elements, and their potential lipid effects

The main purpose of the gastrointestinal tract is to digest foodstuffs, absorb nutrients, and expel waste. The previous section described digestion of food, which is important in understanding the potential mechanisms of action of bariatric procedures. Also relevant is an understanding of vitamin, minerals, and trace element absorption, as well as the location of nutrient absorption. Vitamins are essential organic compounds that cannot be synthesized in the body. Vitamins are derived from plant and animal foods, and necessary for metabolic processes, such as serving as a nonprotein facilitator (coenzyme) for protein enzymes. Minerals (e.g., calcium, phosphorous, magnesium, potassium, and sodium) are nonorganic substances necessary for important biological processes (e.g., vital part of an enzyme). Trace elements (e.g., iron, cobalt, zinc, selenium, molybdenum, and iodine) are nonorganic substances required by the body for biological functions (e.g., vital

Table 5
Potential lipid effects of selected vitamins deficiencies that sometime occur with bariatric procedures*

Vitamins, minerals, trace elements	General description of potential postsurgical deficiency	Effect on lipid levels	References
Vitamin A (retinol/betacarotene) • Vitamin A deficiency is rarely reported after laparoscopic adjustable gastric banding, gastric sleeve, or Roux-en-Y gastric bypass. • Vitamin A deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. • Vitamin A deficiency is reasonably common with biliopancreatic diversion/duodenal switch. • Retinol levels are often routinely monitored after biliopancreatic diversion/duodenal switch. • Table 7 describes treatment of Vitamin A deficiency.	Vitamin A is an essential fat-soluble nutrient important for vision. Its deficiency may lead to night blindness. Vitamin A also is involved with adipocyte function, as well as lipid and possibly glucose metabolism.	Excessive vitamin A (carotenoids such as isotretinoin) may worsen adiposopathy, which contributes to dyslipidemia. Reports of vitamin A deficiency on lipid levels vary, ranging from increased lipid levels, to decreased lipid levels, to no change in lipid levels. Vitamin A deficiency may accelerate atherogenesis, which may be somewhat reversed with vitamin A replacement.	[1,175–184]
Vitamin B1 (thiamine) • Preoperative thiamine deficiency is more common in blacks and Hispanics. • Vitamin B1 deficiency is sometimes reported after laparoscopic adjustable gastric banding, gastric sleeve, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch. • Vitamin B1 deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. • The risk of thiamine deficiency may be increased with postoperative vomiting. • Postoperative thiamine levels are sometimes routinely monitored. • Table 7 describes treatment of thiamine deficiency.	Vitamin B1 / thiamine is an essential water-soluble nutrient involved in many cellular processes, including mitochondrial function (fatty acid oxidation). Deficiency is known as *beriberi,* a word derived from a Sinhalese phrase meaning "weak, weak," which may clinically present as weakness. "Dry" beriberi includes Wernicke-Korsakoff encephalopathy (e.g., ophthalmoplegia, dementia, ataxia, amnesia, etc.); "wet" beriberi includes congestive heart failure. Although mainly described in areas wherein the thiamine in cereal grains are washed away, beriberi is now mostly found in those who may poorly absorb this vitamin, such as patients with alcoholism, and rarely after bariatric surgery. Treatment may require urgent intravenous replacement.	Some reports suggest reduced thiamine levels among patients with diabetes are associated with elevated cholesterol and triglyceride levels. Other reports in experimental diabetes mellitus suggest high-dose thiamine therapy may improve dyslipidemia.	[175,181–183,185–188]
Vitamin B2 (riboflavin) • Vitamin B2 deficiency is rarely reported after laparoscopic adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch. • Vitamin B2 deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. • Postoperative riboflavin levels are usually monitored only if signs and symptoms of deficiency.	Vitamin B2 / riboflavin is an essential water-soluble nutrient involved with many cellular processes, including lipid metabolism (e.g., fatty acid metabolism and cholesterol synthesis). Its deficiency may cause a distinctive bright pink tongue, cracked lips, throat swelling, scleral erythema, low red blood cell count, coma, and death.	During high-fat dietary intake, moderate riboflavin deficiency may increase liver triglycerides and cholesterol, with decreased lipid blood levels. Riboflavin deficiency may promote endoplasmic reticulum stress and impair secretion of apolipoprotein B 100 in the liver.	[175,181–183,189–191]
Vitamin B3 (niacin) • Vitamin B3 deficiency is rarely reported with laparoscopic adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch. • Vitamin B3 deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. • Postoperative niacin levels are usually monitored only if signs and symptoms of deficiency.	Vitamin B3 / niacin is an essential water-soluble nutrient highly expressed in adipose tissue. Its deficiency is known as *pellagra,* which is a word derived from the Italian *pelle* ("skin") and *agra* ("sour"). Presentation includes the "4 Ds" of *d*iarrhea, *d*ermatitis, *d*ementia, and *d*eath. Mainly located in sun-exposed areas, the dermatologic manifestations include ethythema, desquamation, scaling, and keratosis.	Superphysiologic dosages of niacin are used to treat dyslipidemia, with substantial decreases in triglyceride, increases in high-density lipoprotein cholesterol, and modest decreases in low-density lipoprotein cholesterol. Acute administration of niacin inhibits free fatty acid release from adipocytes, which is an effect that diminishes with prolonged treatment. Although superphysiologic doses of niacin may reduce hyperlipidemia, it is unclear that niacin deficiency (e.g., pellagra) increases hyperlipidemia, in part, because of associated impaired intestinal nutrient	[175,181–183,192–194]

Table 5
Continued.

Vitamins, minerals, trace elements	General description of potential postsurgical deficiency	Effect on lipid levels	References
		absorption as a result of niacin deficiency–related diarrhea.	
Vitamin B5 (pantothenic acid) ● Vitamin B5 deficiency is rarely reported with laparoscopic adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch. ● Vitamin B5 deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. ● Postoperative pantothenic acid levels are usually monitored only if signs and symptoms of deficiency.	Vitamin B5 / pantothenic acid is an essential water-soluble nutrient used to synthesize coenzyme-A, as well as proteins carbohydrates and fats. *Pantothenic acid* is derived from a Greek word meaning "from everywhere," is found in most foods, and its deficiency may cause numerous, wide-ranging adverse effects, such as paresthesias and many other signs and symptoms.	Mild pantothenic acid deficiency may increase triglyceride and free fatty acids levels. Pantothenic acid deficiency may increase liver fat, which may improve with pantothenic acid administration.	[175,181–183,195,196]
Vitamin B6 (pyridoxine) ● Vitamin B6 deficiency is rarely reported with either laparoscopic adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch. ● Vitamin B6 deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. ● Postoperative pyridoxine levels are usually monitored only if signs and symptoms of deficiency.	Vitamin B6 / pyridoxine is an essential water-soluble nutrient important for nutrient metabolism and neurologic function. Pyridoxine deficiency can cause skin eruptions resembling seborrheic dermatitis, intertrigo, atrophic glossitis, angular cheilitis, conjunctivitis, sideroblastic anemia, and neurologic symptoms (e.g., somnolence, confusion, and peripheral neuropathy).	Pyridoxine deficiency may decrease omega-3 and omega-6 polyunsaturated fatty acid concentrations.	[175,181–183,197]
Vitamin B7 / H (biotin) ● Vitamin B7 deficiency is rarely reported with laparoscopic adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch ● Vitamin B7 deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. ● Postoperative pyridoxine levels are usually monitored only if signs and symptoms of deficiency.	Vitamin B7 / biotin is an essential water-soluble nutrient important in fatty acid synthesis, amino acid catabolism, and gluconeogenesis. Biotin is usually produced in more than adequate amounts by intestinal bacteria. Its deficiency causes hair loss, conjunctivitis, scaly/erythematous rash around the eyes, nose, mouth, and genital area, anemia, and central/peripheal nervous system disorders. It is a deficiency that can be exacerbated by consumption of raw eggs, which bind this vitamin, making it relatively inactive.	Biotin deficiency may increase in some odd-numbered, long chain saturated fatty acids (15:0 and/or 17:0), which are the same fatty acids often found in dairy fat, and which are broken down into acetyl-CoA and priopionyl-CoA (even numbered fatty acids are metabolized to 2 aceytyl-CoAs). The clinical implications of increased levels of odd-numbered, long chain, saturated fats (as found in dairy products) on cardiovascular disease risk is unclear.	[175,181–183,199–202]
Vitamin B9 (folic acid) ● Vitamin B9 deficiency is sometimes reported with laparoscopic adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch. ● Vitamin B9 deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. ● Postoperative folic acid levels (red blood cell folate) are often routinely monitored. ● Folic acid supplements are often administered after bariatric surgeries, especially in premenopausal, menstruating women of childbearing potential. ● Table 7 describes treatment of folate deficiency.	Vitamin B9 / folic acid is an essential water-soluble nutrient absorbed in the duodenum and proximal jejunum, whose deficiency may cause megaloblastic anemia, as well as loss of appetite and weight loss.	Folate deficiency may lead to elevated levels of homocysteine, which is a risk factor for atherosclerotic cardiovascular disease. Increased homocysteine blood levels may increase liver (but not blood) levels of cholesterol and triglycerides, perhaps resulting in hepatosteatosis. Homocysteine blood levels may correlate to the severity of liver damage among those with nonalcoholic fatty liver disease. Although B vitamins may reduce homocysteine levels, clinical trials have not supported B vitamins as reducing cardiovascular disease.	[175,181–183,203–205]

Table 5
Continued.

Vitamins, minerals, trace elements	General description of potential postsurgical deficiency	Effect on lipid levels	References
Vitamin B12 (cyanocobalamin) ● Vitamin B12 deficiency is commonly reported with laparoscopic adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch. ● Vitamin B12 deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. ● Postoperative vitamin B12 levels are often routinely monitored. ● Vitamin B12 supplements are often administered after bariatric surgeries. ● Table 7 describes treatment of B12 deficiency.	Vitamin B12 / cyanocobalamin is an essential water-soluble nutrient cleaved from its protein by the hydrochloric acid in the stomach, then combined with a protein called intrinsic factor, and then absorbed in the terminal ileum. Vitamin B12 deficiency may induce sterol regulatory element binding protein mediated cholesterol biosynthesis and impaired metabolism of odd-chain fatty acids. Vitamin B12 deficiency may also cause megaloblastic anemia and contribute to central nervous system disorders.	Cyanocobalamin deficiency may increase tissue levels of odd-numbered fatty acids, as well as result in adiposopathic alterations in fat deposition (visceral adiposity), with increases in adipocyte cholesterol, and increases in low-density lipoprotein cholesterol blood levels.	[175,181–183,206–208]
Vitamin C ● Vitamin C deficiency is rarely reported with laparoscopic adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch. ● Vitamin C deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. ● Postoperative vitamin C levels are usually monitored only if signs and symptoms of deficiency.	Vitamin C is an essential water-soluble nutrient is a cofactor from many enzymatic processes; its antioxidant properties are of unclear therapeutic significance. Vitamin deficiency is known as scurvy, and first described among sailors who spent a long time at sea, who would only carry nonperishable meats and dried grains and limited fruits and vegetables. Signs and symptoms include lethargy, weight loss, dry hair and skin, bruising, bleeding gums, loss of teeth, fever, and death. British sailors would consume limes to prevent this vitamin deficiency and were nicknamed "limeys."	Vitamin C deficiency may contribute to hypercholesterolemia and compromise vascular collagen deposition and may increase the risk of atherosclerotic cardiovascular disease events.	[175,181–183,209–213]
Vitamin D ● Vitamin D deficiency is common among preoperative patients with overweight or obesity. ● Vitamin D deficiency is rarely reported to worsen with laparoscopic adjustable gastric banding. ● Vitamin D deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. ● Vitamin D deficiency sometimes occurs with sleeve gastrectomy and Roux-en-Y gastric bypass and commonly occurs with biliopancreatic diversion/duodenal switch. ● After bariatric procedures, 25-hydroxy-(OH)-vitamin D, calcium, phosphorous, and parathyroid hormone are often monitored postoperatively. ● Calcium and vitamin D supplements are commonly administered after bariatric surgeries. ● Table 7 describes treatment of vitamin D deficiency.	Vitamin D is an essential fat-soluble nutrient important for calcium metabolism (and other minerals), bone health, and adipocyte function. Its deficiency may result in decreased bone mineralization, osteopenia, secondary hyperparathyroidism, and hypocalcemia. Vitamin D is important for adipocyte function via intracellular calcium mediated signaling, thus affecting adipocyte function. Vitamin D deficiency may be associated with statin-associated myalgias; however, confirmatory, controlled, randomized, blinded, clinical trials are necessary to determine if vitamin D supplementation reduces statin-associated myalgias.	Lower vitamin D levels are associated with increased total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels and with decreased high-density lipoprotein cholesterol.	[1,175,180–184,214–217]
Vitamin E ● Vitamin E deficiency is only rarely reported with laparoscopic adjustable	Vitamin E is an essential fat-soluble nutrient important for antioxidant and enzymatic activities, and gene expressions, as well as	Vitamin E deficiency may not affect lipid blood levels. Vitamin E replacement in vitamin E–deficient hyperlipidemic patients	[175,180–184,218–221]

Table 5
Continued.

Vitamins, minerals, trace elements	General description of potential postsurgical deficiency	Effect on lipid levels	References
gastric banding, sleeve gastrectomy, or Roux-en-Y gastric bypass. ● Vitamin E deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. ● Vitamin E deficiency may more often occur in patients undergoing biliopancreatic diversion/duodenal switch. ● Alpha-tocopherol levels are often routinely monitored after biliopancreatic diversion/duodenal switch. ● Table 7 describes treatment of vitamin E deficiency.	neurologic function and adipocyte function. Vitamin E deficiency may cause neuropathy and ataxia. Vitamin E may inhibit oxidation of low-density lipoproteins and downregulate CD36 scavenger receptor gene expression in subendothelial vascular macrophages and smooth muscle, decreasing the uptake of low-density lipoproteins.	may be important toward reducing the risk of atherosclerosis.	
Vitamin K ● Vitamin K deficiency is rarely reported with laparoscopic adjustable gastric banding, sleeve gastrectomy, or Roux-en-Y gastric bypass. ● Vitamin K deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. ● Deficiency reasonably common with biliopancreatic diversion/duodenal switch. ● Prothrombin time is often routinely measured after biliopancreatic diversion/duodenal switch. ● Table 7 describes treatment of vitamin K deficiency.	Vitamin K is an essential fat-soluble nutrient important for blood coagulation. This vitamin deficiency may cause bruising and uncontrolled bleeding. The effect of vitamin K on adipocyte function is largely unknown.	Vitamin K deficiency may not affect lipid blood levels. However, vitamin K deficiency may increase arterial calcification, and vitamin K deficiency may be associated with an increased risk of atherosclerosis. Vitamin K antagonists may accelerate atherosclerotic calcification and induce vulnerable plaques.	[175,180–184,222–224]

*Many of these observations are from animal studies or from uncontrolled and unconfirmed observational human studies. See references. The effects of vitamin or mineral supplementation intended to replace deficiencies should not be assumed to have the same effects as vitamin or mineral supplements to those without deficiencies, who may achieve superphysiologic (and potentially toxic) levels.

part of an enzyme), but only in minute amounts. Regarding location of absorption, the stomach represents the location for substantial absorption of water and alcohol. The duodenum is especially important for absorption of fatty acids, amino acids, some minerals (e.g., iron and calcium, especially during calcium deficiency). Largely because of its length and location, the jejunum absorbs the greatest amount of fatty acids, simple sugars, and amino acids, as well as most minerals (e.g., calcium) and vitamins. The ileum is a location important for absorption of bile salts and vitamin B12, as well as some vitamins and minerals. Finally, the colon absorbs some water, sodium chloride, potassium, and intestinally derived vitamin K. Bariatric procedures often involve the manipulation of the location of gastrointestinal tract nutrient absorption, which may directly affect absorbed nutrient quantity and quality; both can affect lipid blood levels.

The American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery have issued guidelines toward the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. This guideline includes a checklist of items to monitor (including vitamins and mineral assessments) based on the type of bariatric procedure (laparoscopic gastric banding, laproscopic sleeve gastrectomy, Roux-en-Y gastric bypass, and biliopancreatic diversion with duodenal switch) as well as the timing for such assessments [174]. In general, postprocedure micronutrient malabsorption deficiencies in vitamins, minerals, and trace elements are more common with bariatric procedures that involve intestinal resection, with relocation of intestinal connections. Thus, so-called malabsorptive procedures such as gastric bypass and biliopancreatic diversion/duodenal switch are reported to have a greater risk for postprocedure deficiencies in vitamins, minerals, and trace elements than laparoscopic adjustable gastric banding [175]. In general, although multivitamin supplementation is recommended for all bariatric procedures, laparoscopic adjustable gastric banding has among the lowest rate of postoperative micronutrient deficiency. Sleeve gastrectomy also has a low rate of postoperative micronutrient deficiency, although monitoring of selected vitamins, minerals, and trace elements are often performed. Roux-en-Y gastric bypass has a higher rate of postoperative

Table 6
Potential lipid effects of selected minerals and trace element deficiencies that sometime occur with bariatric procedures*

Minerals and trace elements	General description of potential postsurgical deficiency	Effect on lipid levels	References
Calcium • Calcium deficiency is rarely reported with laparoscopic adjustable gastric banding. • Relative calcium deficiency is sometimes reported with gastric sleeve or Roux-en-Y gastric bypass, when assessed by elevated parathyroid levels (even if calcium levels are within normal limits). • Calcium deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. • Calcium deficiency commonly occurs with biliopancreatic diversion/duodenal switch. • Although calcium levels may not be decreased in patients with all overweight or obesity who undergo bariatric surgery, vitamin D deficiency may be present. Therefore, 25-hydroxy-(OH)-vitamin D, calcium, phosphorous, and parathyroid hormone are often monitored postoperatively. • Calcium and vitamin D supplements are commonly administered after bariatric surgeries. • Table 7 describes treatment of calcium deficiency.	Calcium is an essential mineral necessary for proper nerve transmission, muscle contraction, bone structure, and cellular function. Concurrent magnesium deficiency may worsen hypocalcemia by impairing parathyroid secretion. (Hypomagnesemia may also promote hypokalemia.) Calcium deficiency may result in decreased bone mineralization, osteopenia, and secondary hyperparathyroidism. Severe hypocalcemia after parathyroidectomy/thyroidectomy can lead to tetany (e.g., muscle contractions, spasms, paresthesias). Calcium is also important for adipocyte lipid metabolism.	In animals, calcium deficiency may increase low-density lipoprotein cholesterol and promote atherosclerosis and aortic calcification. Hypocalcemia in certain settings, such as renal failure with hyperphosphatemia, are associated with arterial calcification. After bariatric surgery, coronary calcification may be reduced, likely reflecting improvement in multiple cardiovascular disease risk factors, independent of effects on low-density lipoprotein cholesterol levels.	[1,111,175,181–183,225–230]
Copper • Copper deficiency is only rarely reported with laparoscopic adjustable gastric banding, gastric sleeve, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch. • Copper deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. • Postoperative copper levels are usually monitored only if signs and symptoms of deficiency.	Copper is a trace element absorbed from the small intestine, and its deficiency (which may accompany iron deficiency) may be clinically manifested by anemia, neuropathies, difficulty walking, increased muscle tone or spasticity, and cardiomegaly. Copper is important for lipid metabolism.	In animals, copper deficiency may result in hyperlipidemia and increased atherosclerosis.	[175,181–183,231–236]
Iron • Iron deficiency is only rarely reported with laparoscopic adjustable gastric banding. • Iron deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. • Iron deficiency commonly occurs with gastric sleeve, Roux-en-Y gastric bypass and biliopancreatic diversion/duodenal switch. • After bariatric procedures, iron, ferritin, transferrin, and total iron binding capacity are often monitored postoperatively. • Iron supplements are often administered after bariatric surgeries, especially among	Iron is a trace element and is normally absorbed in the duodenum and jejunum of the intestine; its deficiency can result in microcytic anemia (possibly manifested clinically by pica), with low iron levels, low ferritin levels, and increased transferrin or total iron binding capacity. Iron is an essential cofactor in many proteins and redox enzymes, involved in a number of biologic processes, including lipid metabolism.	In patients with iron deficiency anemia, triglyceride and very low density lipoprotein cholesterol may be increased, whereas high-density lipoprotein cholesterol and low-density lipoprotein cholesterol may be decreased – which responds to iron replacement therapy.	[175,181–184,237–239]

Table 6
Continued.

Minerals and trace elements	General description of potential postsurgical deficiency	Effect on lipid levels	References
premenopausal, menstruating women of childbearing potential. • Table 7 describes treatment of iron deficiency.			
Selenium • Selenium deficiency is rarely reported after laparoscopic adjustable gastric banding, gastric sleeve, Roux-en-Y gastric bypass, or biliopancreatic diversion/duodenal switch. • Selenium deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. • Postoperative selenium levels are usually monitored only if signs and symptoms of deficiency.	Selenium is a trace element that helps protect cells from free radical damage. Its deficiency may cause cardiomyopathy (Keshan disease). Selenium may be important for low-density lipoprotein receptor function.	Selenium deficiency may contribute to hypercholesterolemia. Selenium supplementation may reduce low-density lipoprotein particle oxidation and attenuate atherosclerosis.	[175,181–183,231,240,241]
Zinc • Zinc deficiency is rarely reported after laparoscopic adjustable gastric banding. • Zinc deficiency can be mitigated with adherence to appropriate nutrition and a high-quality multivitamin supplement. • Zinc deficiency sometimes occurs with sleeve gastrectomy, Roux-en-Y gastric bypass and is common with biliopancreatic diversion/duodenal switch. • Postoperative zinc levels are usually monitored only if signs and symptoms of deficiency. • Table 7 describes treatment of zinc deficiency.	Zinc is a trace element and is important for intestinal mucosal function. Its deficiency can cause poor wound healing, hair loss, acrodermatitis enteropathica–like rash, taste alterations, glossitis, and impaired folate absorption (potentially contributing to folic acid deficiency). Zinc is important for lipid metabolism.	Animal studies suggest severe zinc deficiency can cause an increase in total cholesterol and low-density lipoprotein cholesterol and a decrease in triglyceride levels. Zinc supplements in humans without zinc deficiency do not appear to alter lipid blood levels.	[175,181–183,231,242–244]

*Many of these observations are from animal studies, or from uncontrolled and unconfirmed observational human studies. See references. The effects of vitamin or mineral supplementation intended to replace deficiencies should not be assumed to have the same effects as vitamin or mineral supplements to those without deficiencies, who may achieve superphysiologic (and potentially toxic) levels.

micronutrient deficiency, and selected vitamins, minerals, and trace elements are routinely performed. Finally, biliopancreatic diversion/duodenal switch has among the highest rate of postoperative micronutrient deficiency, and selected vitamins, minerals, and trace elements are routinely performed. In the absence of signs or symptoms of deficiency, and in addition to complete blood cell count, general blood chemistries (including liver enzymes and glucose levels), and lipid profile, the vitamin, mineral, and trace element levels most commonly evaluated after bariatric surgery include thiamine, folate, vitamin B12, 25-hydroxyl-(OH)-vitamin D, parathyroid hormone, calcium, phosphorous, magnesium, iron, and ferritin, with most of these applicable in detecting potential causes of postoperative anemia. Postoperative dual-energy X-ray (DEXA) is also sometimes performed to assess bone mineral density and body composition.

Postbariatric procedure vitamin, mineral, and trace element deficiencies, and their effects on lipid levels, are described in Tables 5 [1,175–224] and 6 [1,111,175,181–184,225–244]. It is challenging to predict how bariatric procedures may affect lipid levels in patients with postoperative micronutrient malabsorption of vitamins, minerals, and trace elements from the intestine. That is because micronutrient deficiencies are often present before bariatric procedures (e.g., vitamin D), and because postoperatively, if 1 vitamin, mineral, or trace elements is deficient, then it is likely the underlying malabsorptive state is affecting other vitamins, minerals, and trace elements as well. Given that different vitamins, minerals, and trace elements may

Table 7
Replacement of select postoperative vitamin and mineral deficiency [245]*

Vitamin/mineral	Assessment	Replacement of deficiency
Vitamin A	Retinol	If corneal keratinization, ulceration, or necrosis: 50–100,000 IU IM for 3 days, followed by 50,000 IU IM for 2 weeks If no corneal changes: 10–25,000 IU orally for 1–2 weeks Further treatment depends on persistent malabsorptive effects, as may most be a concern with biliopancreatic diversion/duodenal switch.
Vitamin B1 (Thiamine)	Thiamine	If hyperemesis, then 100 mg intravenous for 7 days, then 50 mg/d until thiamine in the normal range
Vitamin B9 (Folate)	Red blood cell (RBC) folate	If the daily multivitamin has 400 μg of folic acid, then a typical folic acid replacement dose for deficiency is an additional 800 μg/d orally (total of 1200 μg/d of folic acid) until RBC folate in the normal range, and then a quality multivitamin with at least 400 μg/d of folic acid
B12 (Cobalamin)	Vitamin B12	A typical dose to treat B12 deficiency is 1000 μg/mo IM, 1000 μg/wk sublingually, or 350–500 μg/d orally until B12 in the normal range
Vitamin D	25-hydroxyl-(OH)-vitamin D [1,246]	A typical dose of mild deficiency of vitamin D is 1000 IU/d after gastric bypass and 2000 IU/d after biliopancreatic diversion/duodenal switch For severe deficiency, a single dose of vitamin D 50,000 IU/wk orally can be given until vitamin D levels in the normal range, then 3000 IU if still with substantial malabsorptive signs and symptoms, or if stable, 1000 IU/d after gastric bypass and 2000 IU/d after biliopancreatic diversion/duodenal switch Regarding formulation, vitamin D2 (ergocalciferol) is a form of dietary vitamin D found in plants. Vitamin D3 (cholecalciferol) is found in foods of animal origin and is similar to the vitamin D3 generated when 7-dehydrocholesterol in the skin is converted by ultraviolet radiation from sunlight. Both D2 and D3 are reported as 25-hydroxyvitamin D, which is then converted by the kidneys into the more active 1,25 dihydroxyvitamin D (calcitriol). Vitamin D3 (cholecalciferol) may be preferred (longer half-life and potentially more potent) than vitamin D2 (ergocalciferol). Although the most potent, calcitriol is more rarely used (.25 or .50 mcg/d orally).
Vitamin E	α-Tocopherol	A typical dose to treat vitamin E deficiency is 400 to 800 IU/d orally.
Vitamin K	Prothrombin time	If vitamin K deficiency occurs during substantial gastrointestinal malabsorption, then vitamin K can be replaced 10 mg by slow intravenous route. Otherwise, a typical oral replacement dose is 300 μg/d. Continued treatment depends on persistent malabsorptive effects, as may most be a concern with biliopancreatic diversion/duodenal switch.
Calcium	Calcium	In addition to ensuring adequate vitamin D, calcium deficiency is typically treated with calcium citrate 1200–1800 mg/d. Calcium citrate may be better absorbed than calcium carbonate. Calcium should be taken at least 1 hour apart from other supplements, especially iron.
Iron	Ferritin, iron, total iron binding capacity	For moderate deficiency, total iron intake might typically be 150–200 mg/d elemental iron (325 mg of ferrous sulfate 3 times per day provides 195 mg elemental iron per day). Iron should be taken at least 1 hour apart from calcium. For mild deficiency, women who are menstruating, or patients at risk for iron deficiency anemia, total elemental iron intake (including iron in the multivitamin) should be 50–100 mg/d. Minimum iron supplementation should be 18 mg/d, which may be more effective with vitamin C supplementation 500 mg/d. For severe deficiency, intravenous iron is sometimes required, which is provided in multiple different formulations, some which require test doses.
Zinc	Zinc	A typical replacement dose for zinc deficiency is 60 mg of elemental zinc twice daily. Zinc consumption may impair copper absorption, thus 1 mg of copper should be given per each 10 mg of zinc administered. Once zinc is in the normal range, if malabsorption remains a risk, a typical supplement dose is zinc 30 mg/d.

*High-quality multivitamins are routinely recommended after bariatric procedures, irrespective of deficiencies, which are often recommended to be chewable or liquid. Other routine supplements often include vitamin B12 (500 μg/d tablet or sublingual, or 1000 μg/mo IM), iron (at least 27 mg of elemental iron daily, with at least 500 mg vitamin C), and calcium citrate (1200 mg/d, preferably with vitamin D).

facilitate different effects on nutrient metabolism, via different effects on influx, efflux, anabolism, and catabolism, then the effect of multiple vitamin, mineral, and trace element deficiencies will likely have mixed biologic influences on determination of net lipid blood level (some deficiencies may increase lipid levels; others may decrease lipid levels). In cases of both micro *and* macronutrient malabsorption, diminished intestinal nutrient absorption may also substantially affect lipid blood levels. Table 7 describes replacement of select postoperative vitamin and mineral deficiencies [1,245,246]. This may help explain why bariatric procedures may have varied postoperative effects on lipid blood levels, with lipid levels dependent on: (1) postbariatric procedure nutritional and physical activity, (2) caloric intake and other potential effects on macronutrients, (3) hormonal and metabolic effects of bariatric surgery, and (4) the degree by which micronutrient deficiencies are avoided or successfully treated.

Conclusions

Bariatric procedures improve multiple cardiovascular risk factors, including glucose metabolism, blood pressure, factors related to thrombosis, kidney function, adipocyte and adipose tissue function, inflammatory markers, and vascular markers. This helps explain why bariatric procedures may reduce ASCVD risk. Bariatric procedures also improve lipid levels, which is another potential contributor to reduced ASCVD risk. Principles that apply to bariatric procedures and lipid levels include the following: (1) The greater the fat mass loss, the greater the improvement in lipid parameters such as triglycerides and especially LDL cholesterol; (2) bariatric procedures allow for a decrease in the use of drug treatment for dyslipidemia; and (3) after bariatric procedures, HDL cholesterol may transiently decrease for the first 3–6 months after the procedure, which is usually followed by an increase in HDL cholesterol above the baseline value before the bariatric procedure. Finally, data are scarce regarding the effects of bariatric procedures on some of the lipid parameters of most interest to lipidologists, such as non-HDL cholesterol, apolipoprotein B, and lipoprotein particle number and remnant lipoproteins.

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