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Scientific Statement from the National Lipid Association

Lipids and bariatric procedures part 1 of 2: Scientific statement from the National Lipid Association, American Society for Metabolic and Bariatric Surgery, and Obesity Medicine Association: EXECUTIVE SUMMARY

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Abstract: Bariatric procedures often improve lipid levels in patients with obesity. This 2-part scientific statement examines the potential lipid benefits of bariatric procedures and represents contributions from authors representing the National Lipid Association, American Society for Metabolic and Bariatric Surgery, and the Obesity Medicine Association. The foundation for this scientific statement was based on data published through June 2015. Part 1 of this 2-part scientific statement provides 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

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

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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. Included in part 2 of this comprehensive scientific statement will be a review of: (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 risk factors; (4) the effects of bariatric procedures on lipid levels; (5) effects of bariatric procedures on cardiovascular disease; and finally (6) the potential lipid effects of vitamin, mineral, and trace element deficiencies that may occur after bariatric procedures. This document represents the executive summary of part 1.

Adipose tissue, cholesterol metabolism, and lipids

Adipose tissue is the major storage organ for cholesterol and triglycerides. This helps explain why increased adiposity often results in dyslipidemia.[1] In addition to the adverse biomechanical consequences of increased fat mass resulting in clinical disease,[1] an increase in body fat may also result in adipocyte and adipose tissue dysfunction. This adiposopathy (or "sick fat") results from positive caloric balance and sedentary lifestyle in genetically and environmentally susceptible individuals. From an anatomic standpoint, adiposopathy is characterized by adipocyte hypertrophy and visceral fat accumulation. From functional standpoint, adiposopathy is manifested by adipocyte and adipose tissue endocrine and immune dysfunction that both directly and indirectly contributes to metabolic diseases and increased risk of cardiovascular disease (CVD).[2] Table 1 outlines adipocyte and adipose tissue anatomic, functional, histologic, endocrine, and immune abnormalities that reflect adipose tissue dysfunction (adiposopathy) and which may contribute to metabolic diseases such as dyslipidemia. Table 2 describes potential lipid consequences of bariatric procedure effects on adipose tissue anatomy and dysfunction.

Obesity can be defined as: *"A chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences."*[1] Individuals are sometimes described as being metabolically healthy, but obese. However, a substantial minority of patients with obesity have no adverse health consequences, with the actual prevalence of "metabolically healthy but obese" being uncertain, due to a lack of validated definition, and a dependence upon how, and to what degree potential underlying metabolic dysfunctions are assessed.[3,30,31] Depending on the degree of metabolic interactions and crosstalk with other body organs, the dysfunction of adipocyte and adipose tissue physiology described in Table 1 is highly prevalent and contributes to metabolic abnormalities. A commonly observed lipid pattern among patients with overweight or obesity includes a mixed dyslipidemia characterized by increased triglycerides and triglyceride-rich lipoproteins, as well as reduced high-density lipoprotein cholesterol levels, increased low-density lipoprotein (LDL) particle number, and an increased proportion of smaller LDL particles.[16,32] Bariatric procedures may not only reduce body fat in patients who are obese but may also improve markers of adipose tissue dysfunction resulting in favorable effects on metabolic parameters (eg, glucose levels and blood pressure) and improvements in dyslipidemia.[33,34] Although it remains unclear the degree by which improved glucose control reduces atherosclerotic CVD (ASCVD),[35] it is very clear that improvements in dyslipidemia (and high blood pressure) reduce ASCVD risk.[36,37]

The directionality of the lipid effects of weight loss achieved with bariatric procedures is similar to the lipid effects achieved with nutritional weight loss or pharmacologic weight loss.[32] Among dyslipidemic patients with overweight or obesity, weight loss typically reduces triglyceride levels and (after some time of weight stabilization) often increases high-density lipoprotein cholesterol levels. Accompanying these effects are decreased levels of triglyceride-rich lipoproteins, decreased LDL particle number, with a decreased proportion of smaller LDL particles. As with nutritional intervention, physical activity, and pharmacologic intervention, the long-term effect of bariatric procedures on LDL cholesterol levels are sometimes variable, with most evidence suggesting LDL cholesterol reduction is most consistently achieved with substantial weight loss. Improvement in mixed dyslipidemia helps explain the improved ASCVD outcomes observed in patients who undergo bariatric procedures.

Bariatric procedures, cholesterol metabolism, and lipids

- Endocrine factors relevant to lipid influx, synthesis, metabolism, and efflux are described in Table 3[52];

Table 1 Outline of adiposopathic anatomic, functional, histologic, endocrine, and immune changes that may contribute to metabolic diseases such as dyslipidemia among patients with obesity[3]

Anatomic changes

- Adipocyte hypertrophy with variable increases in adipocyte number, as regulated by intracellular proteins
  - Sterol regulatory element–binding protein 1 (SREBP1), which is the human analogue to adipocyte determination and differentiation-dependent factor 1 (ADD1)
  - Peroxisome proliferator–activated receptor (PPAR) gamma
  - CCAAT-enhancer–binding proteins (C/EBPs)
- When adipogenesis (proliferation and differentiation) in peripheral subcutaneous adipose tissue (SAT) is inadequate to store excess energy, this may
  - Further worsen adipocyte hypertrophy of existing adipocytes
  - Contribute to energy overflow with increased circulating blood plasma-free fatty acid levels, increasing other adipose tissue depots, including
    - Visceral adipose tissue (VAT) accumulation
    - Subcutaneous abdominal adipose tissue accumulation
    - Pericardiac adipose tissue accumulation
    - Perivascular adipose tissue accumulation
  - Contribute to energy overflow with increased circulating blood plasma-free fatty acid levels, increasing fatty infiltration and lipotoxicity to
    - Liver, resulting in nonalcoholic fatty liver disease (NAFLD), with subsets including hepatic steatosis, which may contribute to insulin resistance, and nonalcoholic steatohepatitis (NASH), an inflammatory state that may lead to insulin resistance, fibrosis, and cirrhosis
    - Muscle, resulting in intramyocellular triglycerides and insulin resistance
    - Pancreas, resulting in beta cell dysfunction, macrophage infiltration, and β-cell failure
    - Heart, resulting in fat accumulation within cardiomyocytes, mitochondrial dysfunction, inflammation, and cardiac dysfunction
    - Kidney, resulting in renal fat accumulation, immune cell infiltration, increased glomerular capillary wall tension, podocyte dysfunction, focal and segmental glomerulosclerosis, proteinuria, and progressive renal dysfunction

Histologic and functional changes

- Adipocyte and adipose tissue hypoxia because of
  - Growth of adipose tissue beyond vascular supply
  - Inadequate angiogenesis
  - Impaired blood flow
- Increased adipose tissue immune cell infiltration
- Increased adipocyte apoptosis
- Increased reactive oxygen species and oxidative stress
- Extracellular matrix abnormalities
- Intraorganelle dysfunction
  - Mitochondrial stress*
  - Endoplasmic reticulum stress*
- Changes in adipose tissue neural network and innervations

Adiposopathic endocrinopathies resulting from dysfunctional adipocyte and adipose tissue processes involving

- Angiogenesis
- Adipogenesis
- Extracellular matrix dissolution and reformation
- Lipogenesis
- Growth factor production
- Glucose metabolism
- Production of factors associated with the renin-angiotensin system
- Lipid metabolism

(*continued on next page*)

Table 1 *(continued)*

- Enzyme production
- Hormone production
- Steroid metabolism
- Immune response
- Hemostasis
- Element binding (eg, sterol regulatory element–binding proteins, calcium)
- Multiple receptors, such as receptors for traditional peptides and glycoprotein hormones, receptors for nuclear hormones, other nuclear receptors, receptors for cytokines or adipokines with cytokine-like activity, receptors for growth factors, and catecholamine receptors

Adiposopathic immunopathies resulting from dysfunctional adipocyte and adipose tissue processes involving

- Proinflammatory adipose tissue factors
  - Factors with cytokine activity
  - Acute-phase response proteins
  - Proteins of the alternative complement system
  - Chemotactic or chemoattractants for immune cells
  - Eicosanoids and prostaglandins
- Anti-inflammatory adipose tissue factors

*Organelle stress is an often reported mechanism by which obesity contributes to metabolic disease.[4] "Stress" can be defined as a taxing of the ability of an organism or organelle to cope with a dynamic living environment, which otherwise leads to maintaining healthy cellular homeostasis.[5]

- Endocrine factors relevant to lipid influx are described in Table 4;
- Endocrine factors relevant to lipid efflux are described in Table 5 and Table 6
- Immune factors relevant to lipid influx, synthesis, metabolism, and efflux are described in Table 7.

Bariatric procedures, bile acid metabolism, and lipids

Gastric bypass surgery increases circulating bile acids,[106] which may stimulate farnesoid x receptor (FXR) activity. FXR is a nuclear receptor expressed at high levels in the liver and intestine, which is involved with metabolic processes such as bile metabolism. This may help explain how bariatric procedures may improve lipid levels similar to FXR agonists, and help explain why administration of bile acids may reduce triglyceride levels.[107] Lipid mechanistic effects of bariatric procedures can be compared and contrasted with bile acid sequestrants.[53,108] Over 95% of bile acids are normally transported to terminal ileum enterocytes, and through enterohepatic circulation, return to the liver. Binding of bile acids in the intestine with bile acid sequestrants deprives bile acid return to the liver, which upregulates cholesterol 7 alpha hydroxylase (CYP7A1) increases the conversion of cholesterol to bile acids, increases expression of hepatic LDL receptors through increased LDL receptor synthesis, and increases the clearance of LDL and its cholesterol from the circulation. LDL cholesterol levels are therefore reduced. It is true that binding of bile acids in the intestine with a bile acid sequestrant (resin) may increase HMG CoA reductase activity, increase PCSK9 expression, and deactivate or decrease the activity of FXR, all of which may promote increases in cholesterol levels. However, the cholesterol lowering mechanisms of bile acid sequestration dominate the potential for increasing cholesterol blood levels. A reduction in FXR activity will also increase hepatic triglyceride production, which is a contributing reason why bile acid sequestrants are known to increase triglyceride levels.[53,107,109]

Bariatric procedures, intestinal microbiota, and lipids

Obesity, microbiome, bariatric procedures, and lipids

Individuals with obesity may have altered microbiota compared with lean individuals, which may contribute to decreased bile acid blood levels,[110] increased inflammation,[111] and altered gut hormones.[111] Studies support that microbiota transplanted from obese mice to germ-free mice promotes fat accumulation.[112] When fecal microbiota are transplanted from human twins discordant for obesity

Table 2 Potential lipid consequences of bariatric procedure effects on adipose tissue anatomy and dysfunction in patients with obesity

Factors relative to lipid metabolism	Description	Effect of bariatric procedures	References
Adipose tissue anatomy			
Adipocyte number	During positive caloric balance, limitations in adipogenesis (fat cell proliferation and differentiation) in peripheral subcutaneous adipose tissue may contribute to adipocyte hypertrophy of existing fat cells, adipose tissue dysfunction, and metabolic disease. Conversely, an increase in subcutaneous adipocyte number correlates to decreased TG levels, increased HDL cholesterol levels, increased insulin sensitivity, and decreased insulin levels.	Although bariatric surgery clearly reduces fat cell volume, it is unclear that bariatric surgery (or other methods of weight loss) reduces adipocyte number.	6–14
Adipocyte size	If during positive caloric balance, adipogenesis is impaired, then existing fat cells may undergo hypertrophy, which is an anatomic finding of adiposopathy. Adipocyte dysfunction contributes to metabolic diseases such as dyslipidemia and fatty liver (with or without elevated liver transaminases).	Bariatric surgery may reduce adipocyte size, which may improve adipocyte function and metabolic diseases such as dyslipidemia, high glucose levels, and fatty liver (at least partially due to improved insulin sensitivity), possibly involving an adipocyte volume threshold.	6,15–19
Subcutaneous adipose tissue	Positive caloric balance increases fat deposition in multiple fat depots, with adipose tissue dysfunction in these depots (including subcutaneous adipose tissue) promoting metabolic diseases such as dyslipidemia.	Bariatric surgery reduces subcutaneous fat cell volume. Compared with a reduction in total fat mass, a reduction in subcutaneous adipocyte size improves adipocyte function and more strongly associates with improved insulin sensitivity. This is a mechanism that helps explain how bariatric surgery improves dyslipidemia and nonalcoholic fatty liver disease.	3,6,15
Visceral adipose tissue	Positive caloric balance increases fat deposition in multiple fat depots, which may promote metabolic diseases such as dyslipidemia. An increase in visceral adipose tissue may be a marker for global fat dysfunction.	Bariatric surgery reduces visceral adiposity and generally improves the components of the metabolic syndrome. Bariatric surgery may reduce waist circumference, reduce TG levels, increase HDL cholesterol levels, and decrease glucose levels and decrease blood pressure.	3,20
Pericardiac and perivascular adipose tissue*	Positive caloric balance increases fat deposition in multiple fat depots, including pericardiac and perivascular adipose tissue, which may directly contribute to atherosclerosis.	Bariatric surgery may reduce paracardial and epicardial fat, with limited effects on myocardial triglycerides. The reduction in epicardial fat volume loss may be more limited in patients with sleep apnea.†	21–24
Adipose tissue (dys) function			
Oxidative stress	Adipocyte hypertrophy can produce mitochondrial and endoplasmic reticulum dysfunction, which in turn promotes oxidative stress.‡ Increased oxidative stress may cause adipocyte dysfunction leading to dyslipidemia.	Bariatric surgery may reduce adiposopathic markers of oxidative stress, which may improve metabolic diseases such as dyslipidemia.	2,25–29

HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

*Pericardial fat may include both paracardial fat (fat around the heart and outside the parietal pericardium) and epicardial fat (similar origin as omental and mesenteric fat, sharing common blood supply with the myocardium).

†Obesity-related sleep apnea is also a potential secondary cause of dyslipidemia.

‡Oxidative stress is an imbalance from the creation of unstable oxygen-free radicals and other reactive oxygen species, relative to the ability to detoxify these species or repair subsequent damage. Oxidative stress shares many of the pathogenic properties of aging.

Table 3 Potential lipid consequences of bariatric procedure effects on adipose tissue endocrine factors in patients with obesity

Adipose tissue endocrine factors	Description	Effect of bariatric procedures	References
Adipogenesis and lipogenesis (SREBP1, PPAR gamma, and C/EBPs)	If during positive caloric balance, adipose tissue adipogenesis is impaired, then this may lead to adiposopathy and metabolic disease such as dyslipidemia.	Bariatric surgery reduces adipocyte fat volume, may not change adipocyte number, and has variably reported effects on adipogenic and lipogenic markers*	8,19,38–41
Angiogenesis	Excessive adipocyte hypertrophy may compromise oxygen delivery to fat cells. Expansion of adipose tissue may exceed vascular supply. Both may result in relative hypoxia and contribute to impaired adipogenesis and other adiposopathic processes leading to dyslipidemia. Obstructive sleep apnea (with hypoxia) may exacerbate adiposopathy, worsening dyslipidemia.	Bariatric surgery reduces adipocyte size and adipose tissue expansion, decreases the relative need for adipose tissue angiogenesis, as reflected by a general reduction in cytokines and hormones having effects on vascular development. Bariatric surgery also reduces potentially detrimental antiangiogenic factors which "play a pathogenic role in human adiposopathy." Improved adipocyte and adipose tissue blood flow and oxygen/nutrient delivery may improve their function and thus improve dyslipidemia.	2,42–44
Extracellular matrix	If during adipose tissue expansion, extracellular matrix remodeling is impaired (due to relative hypoxia or other adipocyte dysfunction), then further adipose tissue expansion may be functionally and physically limited, including an impairment in adipogenesis. Without an adequate ability to store energy in adipose tissue, increased circulating free fatty acids may contribute to dyslipidemia and fatty liver.	Bariatric surgery decreases (the relative need for) extracellular matrix expansion, as reflected by a reduction in factors associated with extracellular matrix remodeling. Reduced adipocyte hypertrophy, reduced adipose tissue expansion, and reduced adipose tissue hypoxia, may improve extracellular matrix remodeling and stability, which may improve adipose tissue function, and thus improve dyslipidemia.	2,45,46
Lipogenesis	Regarding energy storage, capillary lumen lipoprotein lipase interacts with TG-containing lipoproteins, allowing lipolysis of TG to generate free fatty acids for transport and storage in adipocytes. ASP mediates short-term energy clearance by reducing circulating TG levels (stimulates LL activity and insulin secretion) and increasing TG storage (stimulates DGAT and impairs HSL). Regarding metabolism, intra-adipocyte TG lipase and HSL are responsible for over 95% of adipocyte TG lipolysis. Perilipin is an intra-adipocyte regulatory protein that coats lipid storage droplets and protects against lipolysis by HSL.	Bariatric surgery: (1) decreases (the relative need for) LL interactions with TG-rich lipoproteins as reflected by a reduction in LL activity; (2) may reduce ASP, possibly reflecting a decreased need for storage of excessive energy; and (3) while the activity of HSL may not change (being dependent on the net hormonal environment), perilipin activity may be increased by bariatric surgery, inhibiting lipolysis by HSL. Reduced lipid storage in adipocytes and other body organs (such as muscle and liver), may allow for improved storage of existing lipids, which may contribute to the improvement in dyslipidemia with bariatric surgery.	16,47–50
Growth factors	Adipose tissue produces and has receptors for a number of growth factors which influence adipogenesis, extracellular matrix modeling, angiogenesis, adipocyte size, and adipose tissue expansion.	Similar to the effect of bariatric surgery on other hormones that increase with obesity (eg, leptin and insulin), bariatric surgery also decreases (the relative need for) growth factors such as vascular endothelial growth factor. Improvement in adipocyte function improves dyslipidemia.	18,51
Cholesterol enzymes	While SREBP1 regulates adipogenesis and fatty acid lipogenesis (see previous sections), SREBP2 regulates cholesterol synthesis, such as upregulation of the rate-limiting step of intracellular cholesterol synthesis: HMG CoA reductase. Regarding hepatic efflux, cholesterol is esterified by ACAT and then incorporated into very low-density lipoproteins by MTP. Similarly, in the	The effect of bariatric procedures on HMG CoA reductase and esterification enzymes is not well characterized. Weight loss may affect mechanisms that both increase and decrease HMG CoA reductase activity, with variable effects on LDL receptors. This helps explain why mild-to-modest weight loss may have	16,52–59

	intestine, cholesterol is esterified by ACAT and then incorporated into chylomicrons by MTP.	inconsistent long-term effects on low-density lipoprotein cholesterol levels.†	
	Free cholesteryl esterification in peripheral tissues for export to high-density lipoproteins occurs through LCAT.		
Other enzyme production	An increase in adiposity can increase enzymes such as 11 beta-hydroxysteroid dehydrogenase type 1 (especially in visceral adipose tissue), which increases the local conversion of cortisone to cortisol. Glucocorticoids are catabolic hormones that increase lipolysis, decrease lipoprotein lipase, increase free fatty acid release, and may contribute to dyslipidemia.	Bariatric surgery may reduce the ratio of active cortisol to inactive cortisone, which may contribute to an improvement in dyslipidemia.	32,60

ACAT, acyl-CoA-cholesterol acyltransferase; ASP, acylation-stimulating protein; C/EBPs, CCAAT-enhancer–binding proteins; DGAT, diacylglycerol acyltransferase; HMG CoA, hydroxyl-methylglutaryl coenzyme A; HSL, hormone sensitive lipase; LCAT, lecithin cholesterol acyltransferase; LL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein; PPAR, peroxisome proliferator–activated receptor; SREBP1, sterol regulatory element–binding protein 1; TG, triglycerides.

*Some reports suggest patients who have undergone bariatric surgery may have reduced PPAR gamma activity, with the adipogenic capacity of adipose-derived stromal and/or progenitor cells being rendered only slightly different from normal weight individuals. Bariatric surgery may reduce deoxynucleic acid damage to adipose tissue progenitor cells, improve their viability, and extend adipocyte replicative lifespan. Animals undergoing bariatric surgery may have reduced SREBP1 expression. Conversely, other reports suggest bariatric surgery may increase SREBP1 activity. Yet, other reports suggest that weight loss by caloric restriction may increase the adipogenic capacity of preadipocytes, wherein enhanced adipogenesis might not only improve metabolic diseases such as dyslipidemia but also potentially contribute to weight regain after initial weight loss.

†HMG CoA reductase activity may increase with insulin, thyroid hormone, estrogen, impairment of intestinal cholesterol absorption with ezetimibe, or increased conversion of cholesterol to bile acids with bile acid sequestrants. HMG CoA reductase activity may also increase with cellular cholesterol deprivation due to decreased cholesterol consumption as might occur with caloric restriction. HMG CoA reductase activity may decrease with increased cholesterol consumption, fasting, glucagon, and statins (HMG CoA reductase inhibitors). HMG CoA reductase activity may also decrease with reduced insulin levels and increased intestinal absorption efficiency, both of which may occur with weight loss in individuals with increased adiposity.

into germ-free mice, mice receiving fecal microbiota from the lean twin remain lean, whereas the mice receiving fecal microbiota from the twin that was obese quickly increase body weight.[111,113] Transfer of gut microbiota from rats that underwent gastric bypass into germ-free rats resulted in weight loss, possibly related to altered production of short-chain fatty acids.[114]

Typically, the stomach and proximal small intestine have relatively limited amounts of acid-tolerant lactobacilli and streptococci bacteria content[115] because of the bacteriocidal activity of gastric acid. In contrast, the ileum and colon typically have hundreds of trillions of bacteria. The major bacteria phyla of intestinal microbiome are bacteroidetes and firmicutes. The gram-negative bacteroidetes includes about 20 genera, many which may assist with epithelial cell maturation and function.[116] The gram-positive firmicutes (which includes lactobacilli, but mostly the clostridia class) is the largest bacterial phylum.[111] Firmicutes comprises over 200 genera, many of which may more efficiently extract calories from carbohydrates than bacteroidetes through fermentation of indigestible foods into short-chain fatty acids (eg, acetate, butyrate, and propionate) that are absorbed through the intestinal mucosa.[117] These short-chain fatty acids may not only serve as energy sources (increasing absorption of energy that may contribute to positive caloric balance) but also may serve as signaling molecules that affect central nervous system receptors, thus potentially affecting neurobehavior.[118] Among individuals with obesity, firmicutes proportionally increases compared with bacteroidetes.[119,120]

It is not only the content of the microbiome that may affect body weight and metabolic disease, the mere presence of a microbiome may have effects as well. At least in rodents, germ-free mice may be resistant to diet-induced obesity.[121] Compared with germ-free mice, potential mechanisms by which mice with microbiota may increase body fat accumulation[111,121] include: (1) increased density of small intestinal villi capillaries allowing for greater absorption of nutrients; (2) enhanced monosaccharide intestinal uptake through enriched carbohydrate enzymes in the gut (eg, microbial glycoside hydrolases, polysaccharide lyases, and carbohydrate esterases); (3) increased SREBP1 activity, promoting lipogenesis; (4) suppressed secretion of fasting-induced adipose factor (angiopoietin-like protein 4), an effect that may reduce adipose tissue fatty acid oxidation and reduce uncoupling of the process of mitochondrial adipose tissue adenosine triphosphate generation (which may in turn, potentially reduce thermogenesis)[122]; (5) reduced hepatic and muscle fatty acid oxidation; (6) alterations in bile acid metabolism, structure, and signaling, and (7) effects on appetite, satiety (through decreased gut hormones such as glucagon-like peptide 1), and neurobehavior brain centers.[123,124] Bariatric procedures counter many of these obesigenic processes, such as reducing the availability of nutrients delivered to the gut, reducing lipogenic signaling, favorably altering bile

Table 4 Potential lipid consequences of bariatric procedure effects on cellular receptors in patients with obesity

Cellular receptors	Description	Effect of bariatric procedures	References
LDL receptors	LDL receptors are present on the cell surfaces of body tissues and through interaction with hepatically-secreted circulating lipoproteins, allow for the transport of cholesterol from the liver to nonhepatic tissues. When cells are deprived of cholesterol, this is sensed by SREBP2, which increases LDL receptor number/activity. An increase in LDL receptor activity, especially on the liver, increases clearance of LDL and its cholesterol from the blood and reduces LDL cholesterol levels. Conversely, a decrease in LDL receptor activity, decreases clearance of LDL and its cholesterol from the blood and increases LDL cholesterol levels.	Bariatric procedures may impair cholesterol intestinal absorption, which increases hepatic LDL receptor activity, such that more "malabsorptive" bariatric procedures may increase LDL receptor activity more than "restrictive" bariatric procedures, and thus, may therefore have the greatest potential to reduce LDL cholesterol levels.*	16,34,56,61,62
PCSK9	PCSK9 is a serine protease secreted extrahepatically by the liver. Its secretion is the result of increased SREBP2 activity, which simultaneously increases hepatic LDL receptor activity. PCSK9 binds to domains of hepatic LDL receptors, directing the receptor for destruction by intracellular lysosomes. An increase in PCSK9 activity is associated with fewer LDL receptors, increased LDL particles, and thus increased LDL cholesterol levels.	The effects of bariatric surgery on PCSK9 are not well characterized.†	63,64
HDL receptors	SR-B1 is a bidirectional receptor found on numerous cells (eg, such as liver, adipocyte, adrenal, macrophages, and in other tissues) that facilitates the influx of cholesteryl esters from HDLs, and efflux of cholesteryl esters from arterial macrophages to HDL particles. ABCA1 and ABCG1 are unidirectional and help transport free cholesterol from body cells to nascent HDLs.	Bariatric surgery increases efflux of cholesterol via SR-B1 and ABCG1, and increases LCAT activity, all which increase HDL cholesterol levels and HDL mass.	65,66
Fatty acid translocase (CD36) receptors	CD36 is a membrane protein that serves as a class B scavenger receptor, and which binds oxidized LDLs, native lipoproteins, oxidized phospholipids, and long-chain fatty acids. CD36 activity correlates with obesity and insulin resistance. Triglyceride levels may be an independent predictor of CD36 activity. CD36 may be on taste buds, serving as a taste receptor, potentially increasing the attraction for (creamy) fatty foods, and potentially worsening dyslipidemia.‡	Bariatric surgery reduces CD36, which correlates to a reduction in fat mass, truncal fat mass, insulin resistance (improved insulin sensitivity), liver fat, C-reactive protein, and reduced triglyceride levels. Bariatric surgery may increase or decrease taste acuity, which may influence weight maintenance. If bariatric surgery reverses a preoperative preference for energy dense foods (which in addition to the potential role of CD36, may also involve alterations in brain taste reward and addiction centers), then this may improve weight loss maintenance and help maintain improvement in lipid levels.	67–70
PPAR gamma receptors	Adipogenesis and lipogenesis are regulated by SREBP1 and C/EBPs, as well as PPAR gamma, which is a nuclear receptor whose natural ligand includes free fatty acids and eicosanoids. PPAR gamma activity increases with overfeeding. Both PPAR gamma	The effects of bariatric surgery on adipogenesis or makers of adipogenesis are unclear.§	8,16,19,38–41,71,72

and SREBP1 are upregulated with obesity. PPAR gamma agonism promotes adipogenesis, which helps explain how PPAR gamma agonists (thiazoladinediones) may improve glucose and lipid levels and increase subcutaneous adipose tissue.

ABC, adenosine triphosphate–binding cassette transporters; HDL, high-density lipoprotein; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator–activated receptor; SR-B1, scavenger receptor B1, SREBP2, sterol regulatory element–binding protein 2.

*A reduction in lipid blood levels after weight loss is related to increased LDL receptor expression and increased activity of lipoprotein lipase. Given the variability in HMG CoA activity with weight reduction (which may act somewhat independently of LDL receptors), this may help explain that if a clinically meaningful reduction in LDL cholesterol is achieved with weight reduction, it often requires a greater degree of weight loss, compared with weight-lost promoted improvements in other lipid levels (eg, reduction in triglyceride and increase in HDL cholesterol levels).

†Although nutritional interventions such as a Mediterranean-type diet may decrease PCSK9 activity and decrease LDL cholesterol levels, the addition of weight loss to the Mediterranean diet may not result in further changes to PCSK9 or LDL cholesterol. Similarly, as with HMG CoA reductase, some evidence suggests that bariatric surgery may not affect PCSK9 liver expression. This may help explain why weight loss via caloric restriction, weight management pharmacotherapy, and bariatric procedures may have inconsistent effects on LDL cholesterol levels unless substantial weight loss is achieved.

‡CD36 is also involved in a variety of cellular processes involving not just lipid transport, but immune regulation (eg, malaria), hemostasis, adhesion, angiogenesis, and atherosclerosis.

§Some reports suggest patients who have undergone bariatric surgery may reduce PPAR gamma activity, with the adipogenic capacity of adipose-derived stromal/progenitor cells being rendered only slightly different from normal weight individuals. Conversely, other reports suggest bariatric surgery may increase PPAR gamma activity, thus helping to account for improved postoperative insulin sensitivity and glucose levels. Yet, other studies suggest weight loss by caloric restriction may increase the adipogenic capacity of preadipocytes, wherein enhanced adipogenesis might not only improve metabolic diseases such as dyslipidemia, but potentially contribute to weight regain after initial weight loss.

acid metabolism, reducing inflammation, and having favorable effects on gut hormones. In addition, bariatric procedures typically result in a decrease in the firmicutes:bacteroidetes ratio, suggesting that in addition to weight loss, mechanisms accounting for improvement in metabolic diseases (such as obesity and dyslipidemia) may also include favorable alterations in the gut microbiome.[125]

Bile acids, microbiome, bariatric procedures, and lipids

In addition to the gut microbiome potentially promoting obesity, microbiota may also affect bile acid metabolism, which may contribute to dyslipidemia. The relationship between the microbiome and bile acids are interdependent, and the amount and types of bile acids secreted from the liver can help determine the composition of the gut microbiome, at least in part because bile acids (ie, detergents) can disturb bacterial membrane integrity.[126,127] For example, deoxycholic acid may have greater antimicrobial, detergent effects than cholic acid because of its greater lipophilicity for bacterial membranes.[127]

But just as bile acids can affect the gut microbiome, microbiota can also affect bile acids, through alterations in structure. Intestinal bacteria may 7-dehydroxylate the primary bile acids into the secondary bile acids. Gut microbiota may promote bile acid deconjugation, dehydrogenation, and dehydroxylation, increasing the chemical diversity and potential toxicity of intestinal and systemic bile acids.[127,128] The presence of gut microbiota may reduce bile acid levels in the gallbladder and small intestine, increase bile acids in the cecum, colon, feces, and blood, with an overall decrease in bile acid pool.[128] The decrease in overall bile acid pool size with gut microbiota (compared with a germ-free environment) may be due to their deconjugation of primary bile acids, hindering their recirculation[129] and creation of bile acid metabolites that may function as FXR antagonists, thus limiting bile acid synthesis.[128]

Alterations in overall bile acid pool size and composition may affect lipid and glucose metabolism.[129] Bariatric surgery may increase bile acid blood levels.[130] Increased bile acids after bariatric surgery may result in favorable metabolic signaling,[130] such as increased Takeda G protein-coupled receptor 5 (TGR5) and[131] and fibroblast growth factor 19 (FGF) activity,[132] both important for improved glucose metabolism. Bariatric surgery may also increase FXR activity,[130] which as discussed before, has a number of effects that may improve lipid metabolism.

Inflammation, microbiome, bariatric procedures, and lipids

Inflammation, through increased adipocyte immune factors, increased adipose tissue immune cells, and

Table 5 Potential lipid consequences of bariatric procedure effects on other lipid and lipid metabolism factors in patients with obesity

Other lipid and lipid metabolism factors	Description	Effect of bariatric procedures	References
Fatty acids	Increased circulating free fatty acids may promote lipotoxicity of various body organs (such as liver and muscle), resulting in insulin resistance and dyslipidemia. Increase concentration of circulating free fatty acids can be caused by increased VLDL hepatic secretion and subsequent lipolysis, increased intestinal chylomicron secretion and subsequent lipolysis, increased adipocyte lipolysis, and decreased uptake of free fatty acids by body tissues (as regulated by fatty acid–handling proteins such CD36 and fatty acid transport proteins).	Bariatric surgery may ultimately decrease circulating free fatty acids. If bariatric surgery results in rapid weight loss, then similar to starvation or administration of very low calorie diets, the rapid lipid mobilization from fat depots may result in a transient increase in circulating free fatty acids for approximately the first month postoperatively. Thereafter, circulating free fatty acids typically decrease, resulting in less potential for lipotoxicity, improved insulin sensitivity, and improvement in mixed dyslipidemia.	16,69,73–76
Apolipoprotein (apo) A1	ApoA1 is the main protein constituent of HDLs and helps promote free cholesterol efflux from body tissues via the adenosine triphosphate–binding cassette transporters (ABC) A1 and ABC-GI to HDLs. The role of ATP transporters in free cholesterol efflux from adipocytes is described in Table 6.	Bariatric surgery may increase apoA1 (and apoA IV) and HDL cholesterol levels.	16,77
Apolipoprotein (apo) B	One molecule of apoB is found on the outside membrane of each atherogenic lipoprotein. Hence, when apoB levels are increased, this is considered a surrogate marker for an increased number of atherogenic lipoproteins, which is a root cause and driver of atherosclerosis.*	Bariatric surgery may decrease apoB levels, including a reduction in both hepatic apoB 100–containing lipoproteins, and intestinal apoB 48 chylomicron lipoproteins.†	16,32,36,78–81
Apolipoprotein (apo) C	ApoC1 is expressed in tissues such as adipocytes, with overexpression inhibiting the hepatic uptake of VLDL, diminishing the uptake in adipose tissue and increasing TG and cholesterol levels. ApoC3 is a protein component of VLDL, which inhibits lipoprotein/hepatic lipases, impairs hepatic uptake of TG-rich lipoproteins (such as lipoprotein remnants), promotes hypertriglyceridemia, and may contribute to insulin resistance and atherosclerosis.	Bariatric surgery may have little effect in ApoC1, but may substantially reduce ApoCIII, which is accompanied by a reduction in TGs and non-HDL levels.	16,80,82
Apolipoprotein (apo) E	Apo E is found in adipocytes and facilitates adipocyte triglyceride accumulation and cholesterol efflux to HDL particles. Apo E is also present on TG-rich lipoproteins and assists with lipoprotein-binding to receptors on the liver and peripheral cells. Excessive apoE may be a marker of dysfunction of HDL particles. ApoE genotyping may help diagnose the presence of dysbetalipoproteinemia in symptomatic patients with mixed dyslipidemia and allow for presymptomatic risk assessment for type III dysbetalipoproteinemia (apo E2), as well as increased	In humans,‡ excessive apoE in HDL particles may contribute to their dysfunction. Human trials suggest that within the first 6 months during rapid weight loss with bariatric surgery, both HDL cholesterol and apoE decrease. The initial drop in HDL cholesterol levels may reflect the gradual qualitative switch in HDL particles from apoE-containing to more functional apoAI-containing HDL particles. ApoE genotyping (Apo-E3/E4) may predict postbariatric surgery gallstone formation.	16,66,82–87

risk for dementia, Alzheimer's disease, and other neurologic abnormalities (apo E4).

HDL, high-density lipoprotein; TG, triglycerides; VLDL, very low-density lipoprotein.

*Patients with adiposopathic mixed dyslipidemia, as might occur with insulin resistance or type 2 diabetes mellitus, often have an increased number of atherogenic particles relative to the concentration of LDL cholesterol levels, compared with those without diabetes mellitus. This occurs as the result of an increased proportion of smaller LDL particles, and may be assessed by measuring apoB, non-HDL cholesterol, or atherogenic particle number.

†Although apoB levels are typically elevated in individuals who are obese compared with those who are lean, modest-to-moderate weight loss of up to 10% of initial body weight may not significantly reduce apoB levels. This would be consistent with guidelines and statements acknowledging that clinically meaningful reductions in LDL (a major apoB-containing lipoprotein) require greater weight loss in patients who are overweight or obesity, compared with improvements in other lipid parameters such as triglycerides and HDL cholesterol, which may improve with lesser degrees of weight loss (5%–10%).

‡Some mice studies suggest Apo E expression decreases with positive caloric balance and increases with weight loss. However, HDL metabolism differs in mice vs humans.

increased adipose tissue release of adipocytokines, is also an important contributor to adiposopathy and its adverse metabolic consequences.[95,133] Not only does a high caloric dietary intake lead to inflammation of adipose tissue but also may lead to the inflammation of other body tissues, especially the liver, which may also contribute to insulin resistance and fatty liver.[16,111] When assessing the literature on the potential impact of dietary quality on metabolic disease, it is important to note that many of the animal studies evaluating the relationship between diet-induced obesity and inflammation have used general, multipurpose rats (many bred with a predisposition to obesity), which in contrast to being fed "chow" (eg, cereal/plant food diets), are fed "high-fat" diets that often contain 45% to 60% fat (eg, lard).[134] These "high-fat" diets often have high amounts of carbohydrates, which is important when interpreting reported animal data to potential applications in humans. In general, literature reports of increased inflammation with diet-induced obesity in rodents consuming "high-fat" diets might best be interpreted as reflecting the effects of positive caloric balance due to energy dense diets, and not necessarily effects isolated to the increased fat nutrient component, as might be applicable to carbohydrate-restricted nutritional intervention often used in clinical practice.[1] Having said this, excessive consumption of certain types of fats and carbohydrates may have adverse effects, with evidence suggesting that consumption of high amounts of some saturated fats (butter and cream), transfats, and possibly high fructose solutions may have the greatest potential to induce inflammatory responses.[111]

Mechanistically, high-fat (caloric) diets modulate gut microbiota and increase circulating levels of the lipopolysaccharide components of the outer membrane of gram-negative bacteria, either through increased intestinal permeability or uptake into intestine-produced circulating chylomicrons. Lipopolysaccharides induce endotoxemia, which promotes immunologic cytokine responses and insulin resistance ("metabolic endotoxemia").[135] In fact, lipopolysaccharide is sometimes used to induce endotoxemia for research purposes, which may increase immune factor expression of tumor necrosis factor and interleukin 6, and lead to adipose tissue dysfunction and insulin resistance.[136] In addition, bacteria may ferment dietary fibers into short-chain fatty acids, which may not only serve as substrate for gluconeogenesis and lipogenesis but also may increase permeability of the intestinal epithelium, increasing absorption of macromolecules from the intestine, and result in increased systemic inflammatory responses.[129]

Alterations in the function of the gut microbiome, with reductions in lipopolysaccharides, as well as reductions in inflammation, as evidenced by reduced inflammatory markers associated with endotoxemia[137] may contribute to the favorable metabolic benefits of bariatric surgery. Improvement in adipose tissue and other body organ inflammation may improve dyslipidemia[16,95,96] (Table 2).

Table 6 Potential lipid consequences of bariatric procedure effects on transfer or transport proteins in patients with obesity

Transfer or transport proteins	Description	Effect of bariatric procedures	References
Cholesteryl ester-transfer protein (CETP)	CETP is a protein produced by adipocytes (among other tissues), which facilitates the exchange of cholesteryl esters and triglycerides between circulating lipoproteins. CETP is increased with feeding and body weight. An increase in CETP activity may decrease HDL cholesterol, increase levels of LDL cholesterol, and increase the proportion of the smaller (and potentially more atherogenic) LDL particles. CETP inhibitor drugs in development markedly increase HDL cholesterol levels and reduce LDL cholesterol levels.	Bariatric surgery may decrease CETP activity, which is associated with an increase in HDL cholesterol and reduction in hyperlipidemia.	16,32,88–91
Phospholipid transfer protein (PTP)	PTP is a transfer protein produced by adipose tissue (and other body tissues) that catalyzes the exchange of phospholipids from HDL particles to triglyceride-rich lipoproteins. PTP production is increased with increased body fat. PTP's net effect on HDL functionality, peripheral transport, and atherosclerosis is unclear.	Bariatric surgery may decrease PTP activity, although the effects on lipoproteins are unclear.	16,89
Fatty acid transport protein (FATP)	FATPs are a family of adipocyte membrane proteins that not only transport fatty acids but also have the capacity to activate (via acyl-CoA synthetase activity) in preparation for adipocyte fatty acid biosynthesis and storage. Fatty acid handling proteins such as FATP (and CD36, described previously) correlate with obesity and insulin resistance. Insulin can increase FATP expression. If the generation of fatty acids from positive caloric balance exceeds the ability of fatty acid handling proteins to store fatty acids in adipocytes, then this may promote fatty liver and contribute to dyslipidemia.	The effect of bariatric surgery on FATP is unclear.*	16,69
Adenosine triphosphate (ATP)–binding cassette transporter (ABC transporter)	ABCs (eg, ABCA1 and ABCG1) are transporters found on tissue membranes such as adipocytes and hepatocytes, which facilitate the efflux of cholesteryl esters to HDL particles. ABCB11 is found exclusively in liver and is responsible for bile formation and flow.†	Bariatric surgery may increase the cholesteryl ester efflux capacity by increasing the activity of both ABCG1 and scavenger receptor class B type 1. Some reports suggest ABCA1 activity may be decreased. When increased ABCG1 and scavenger receptor class B type 1 activity is coupled with reduced CETP activity, the net result of bariatric surgery over time is an increase in cholesterol-rich HDL, and thus, increase in HDL cholesterol.	16,65,92,93
Glucose transporter (GLUT)-4	GLUT-4 is a glucose transport found in adipocytes and muscle which facilitates glucose transport and promotes lipogenesis. With adiposopathy, larger fat cells may become insulin resistant, thus blunting insulin-mediated glucose transport. The net result may be increased lipolysis, release	Bariatric surgery may upregulate GLUT-4, which may facilitate lipogenesis, and thus, reduce mixed dyslipidemia.	16,72

of free fatty acids, lipotoxicity, dyslipidemia (due to insulin resistance), and hyperglycemia (due to insulin resistance and impaired glucose transport).

CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*After weight loss has stabilized, then the free fatty acid load would be expected to decrease with weight loss bariatric procedures, thus improving fatty acid handling proteins to store circulating fatty acids. Furthermore, a reduction in circulating free fatty acids may increase insulin sensitivity, allow improved fatty acid storage in adipocytes, and improve mixed dyslipidemia.

†If cholesterol stores in adipose tissue are increased with obesity, and if cholesteryl esters undergo efflux from adipocytes to HDL via ABC transporters, then it might be expected that HDL cholesterol levels would be increased with obesity. The fact that obesity is associated with a decrease in HDL cholesterol levels suggests impairment of cholesterol transport via ABC transporters may be impaired. Other potential causes of low HDL cholesterol levels in patients with overweight or obesity include increased free fatty acid fluxes to the liver, exacerbated by overnutrition and increased chylomicron formation, which results in increased hepatic synthesis of very low-density lipoprotein. The effectiveness of lipolytic enzymes such as lipoprotein lipase to maintain normal triglyceride levels may be impaired due to increased competition from elevated concentrations of triglyceride-rich lipoproteins (eg, VLDL and chylomicron and their remnants), coupled with the reduced activity of lipoprotein lipase that often occurs with overweight and obesity. The increase in circulating triglyceride-rich lipoproteins increases the exchange of cholesteryl esters and triglycerides between triglyceride-rich lipoproteins and high HDL particles (as well as LDL particles), which is a process facilitated by CETP (described in the table). Not only does the exchange of cholesterol from HDL to other circulating lipoprotein particles reduce HDL cholesterol levels but also once triglyceride-rich HDL particles undergo lipolysis, HDL particles become smaller and become more susceptible for clearance/metabolism by the kidney, further reducing HDL cholesterol levels.

Gut hormones, microbiome, bariatric procedures, and lipids

In addition to the effects of the gut microbiome on promoting obesity, bile acid metabolism, and inflammation, gut microbiota may contribute to metabolic diseases through altering the signals between the intestine and the brain. Signaling from the brain to the gut occurs through: (1) sympathetic efferent neurons; (2) parasympathetic efferent neurons; (3) neuroendocrine factors involving the adrenal medulla; and (4) neuroendocrine factors involving the adrenal cortex. Signaling from the gut to the brain occurs through: (1) vagal and spinal afferent neurons; (2) immune mediators such as cytokines; (4) gut microbiota–derived signaling molecules; and (4) gut hormones.[138]

The inter-relationship between gastrointestinal hormones, obesity, bariatric surgery, and lipids is discussed more in detail in part 2 of this scientific statement. But in general, bariatric surgery may decrease orexigenic ghrelin and NPY levels, and increase anorexigenic PYY and GLP-1 activity.[139] These hormonal effects may contribute to weight loss with bariatric procedures and improvements in metabolic diseases such as dyslipidemia.

Conclusion

Bariatric procedures reduce body fat and have favorable effects on adipocyte and adipose tissue function, which contributes to improvement in metabolic diseases such as dyslipidemia, high glucose levels, and high blood pressure. Among the mechanisms by which bariatric procedures may improve dyslipidemia includes favorable alterations in endocrine and inflammatory homeostasis. Bariatric procedures may also have favorable effects on bile acid metabolism and the intestinal microbiome, which may also improve dyslipidemia.

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Table 7 Potential lipid consequences of bariatric procedure effects on immune factors in patients with obesity

Immune factors	Description	Effect of bariatric procedures	References
Adiponectin	Adiponectin is an adipocyte hormone and adipokine which is generally sconsidered to be anti-inflammatory and may facilitate insulin sensitivity. Adiponectin levels may be reduced with increased adiposity and adiposopathy. Reduced adiponectin levels are associated with mixed dyslipidemia, reduced lipoprotein lipase activity, and hepatosteatosis.*	Bariatric surgery may increase adiponectin levels. The increase in adiponectin secretion may have anti-inflammatory effects that help improve dyslipidemia, and help account for how bariatric surgery may improve adiposopathy and reduce cardiovascular disease risk.	16,94–97
Leptin	Leptin is an adipocyte hormone and adipokine that is increased with increased adiposity. Increased leptin levels may increase catecholamine release (which increases blood pressure) and have other effects that promote atherosclerosis. Individuals with increased adiposity may have resistance to the satiety effects of leptin, which may be worsened by excessive calories and improved with increased physical activity.	Bariatric surgery may reduce leptin levels. Leptin levels may have some peripheral tissue effects (eg, adipose tissue, liver, and muscle). However, it is likely the main reason a decrease in leptin secretion is associated with improved dyslipidemia is because of the multitude of other metabolic effects of reduced adipocyte size, which is reflected by a reduction in leptin secretion.	16,94–99
Interleukin 6 (see part 2 of this scientific statement)	Interleukin 6 (IL-6) is an adipokine produced by adipocytes. IL-6 is increased with adipocyte hypertrophy, that increases lipolysis and promotes insulin resistance, which may contribute to adiposopathic mixed dyslipidemia. IL-6 also promotes the release of C-reactive protein from the liver.	Bariatric surgery may decrease IL-6 levels, which may improve lipid levels, and thus help account for how bariatric surgery may reduce CRP, improve adiposopathy, and reduce cardiovascular disease risk.	16,100
C-reactive protein (see part 2 of this scientific statement)	C-reactive protein (CRP) is an acute phase reactant that increases with inflammatory disease. In the absence of a definitive rheumatologic condition or ongoing infection, a mild increase in CRP is often considered a biomarker for increased ASCVD risk; inflammation is an important component of atherosclerosis. An increase in body fat can also increase CRP. Although CRP may be released directly from adipose tissue, most of CRP produced from adipose tissue among those overweight or obese is likely from an increase in IL-6 from enlarged adipocytes, which stimulates CRP production from the liver.†	Bariatric surgery may decrease CRP levels, which may correlate with improved adipose tissue function, improved dyslipidemia, and help account for how bariatric surgery may improve adiposopathy and reduce cardiovascular disease risk.†	16,94,100–103
Tumor necrosis factor (see part 2 of this scientific statement)	In adipose tissue, tumor necrosis factor (TNF) is mainly produced by stromal macrophages. TNF may be increased with increased body fat. TNF promotes adipose tissue lipolysis, impairs adipogenesis, and impairs lipogenesis. This may increase circulating free fatty acids and contribute to increase insulin resistance, which may worsen dyslipidemia.	Bariatric surgery has inconsistent reported effects on TNF levels; it is unclear the degree by which bariatric procedures affect lipid levels based on TNF-mediated effects.	16,94,100,104,105

*Adiponectin levels may also be increased with increased physical activity and omega-3 fatty acids.

†An increase in CRP is often reflective of adiposopathic inflammation, which may contribute to adiposopathic mixed dyslipidemia. The reduction in IL-6 and CRP with statins may be partially due to statin-induced reductions in adipose tissue inflammation.

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