

Obesity, adiposity, and dyslipidemia: A consensus statement from the National Lipid Association

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Triglycerides

Abstract: The term “fat” may refer to lipids as well as the cells and tissue that store lipid (ie, adipocytes and adipose tissue). “Lipid” is derived from “lipos,” which refers to animal fat or vegetable oil. Adiposity refers to body fat and is derived from “adipo,” referring to fat. Adipocytes and adipose tissue store the greatest amount of body lipids, including triglycerides and free cholesterol. Adipocytes and adipose tissue are active from an endocrine and immune standpoint. Adipocyte hypertrophy and excessive adipose tissue accumulation can promote pathogenic adipocyte and adipose tissue effects (adiposopathy), resulting in abnormal levels of circulating lipids, with dyslipidemia being a major atherosclerotic coronary heart disease risk factor. It is therefore incumbent upon lipidologists to be among the most knowledgeable in the understanding of the relationship between excessive body fat and dyslipidemia. On September 16, 2012, the National Lipid Association held a Consensus Conference with the goal of better defining the effect of adiposity on lipoproteins, how the pathos of excessive body fat (adiposopathy) contributes to dyslipidemia, and how therapies such as appropriate nutrition, increased physical activity, weight-management drugs, and bariatric surgery might be expected to impact dyslipidemia. It is hoped that the information derived from these proceedings will promote a greater appreciation among clinicians of the impact of excess adiposity and its treatment on dyslipidemia and prompt more research on the effects of interventions for improving dyslipidemia and reducing cardiovascular disease risk in overweight and obese patients.

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Excessive body fat and its metabolic consequences are worldwide epidemics.¹ In the United States alone, more than two-thirds of adults are overweight or obese.² The adverse health consequences of excessive body fat is especially correlated to the dysfunctional deposition of adipose tissue, in that abdominal adiposity measures are directly and significantly associated with mortality.³

Principal among metabolic comorbidities associated with excessive body fat is dyslipidemia. Results from national surveys suggest that dyslipidemias are the most common comorbidities associated with a range of body mass indices (BMI), with substantial increases found with increased body weight (Fig. 1). One of the challenges for patients and clinicians is that excessive body fat is often classified into overweight and obesity on the basis of BMI, and perhaps waist circumference, rather than the degree by which increased body fat promotes illness.⁴ Some have suggested various “staging” categorizations, largely based upon the presence of comorbidities.⁵ For the clinician, the diagnostic problem remains that while BMI cut-off points may be useful from a public health standpoint, substantial individual variability exists in the correlation between excessive body fat and pathologic consequences.⁶ The association between body fat mass and metabolic disease is not absolute, and the diagnosis of obesity is often a poor surrogate for the adverse health risks of increased body fat. Various “obesity paradoxes” describe circumstances wherein an increase in body fat is not always associated with an increase in risk for cardiovascular disease (CVD). In fact, excessive body fat is sometimes associated with decreased CVD risk.⁶ These apparent obesity paradoxes can often be explained by assessing the pathogenic potential of adipose tissue based upon adipocyte

and adipose tissue function and dysfunction rather than on body fat mass alone.⁶ This same basic principle applies to the relationship between adiposity and dyslipidemia. Therefore, for the purposes of defining terms in this discussion, “obesity” is mostly defined as per established classification metrics relative to BMI.⁷ “Adiposity” is defined as the degree of body fat accumulation and is generally used in the present work to denote excess body fat.

Adiposity, adiposopathy, and “adiposopathic dyslipidemia”

The pathogenic potential of adipose tissue

Excess adiposity can incite adipocyte and adipose tissue pathogenic responses that contribute to metabolic diseases. Like obesity, adiposity-related metabolic diseases are also epidemics (eg, type 2 diabetes mellitus [T2DM], high blood pressure, dyslipidemia, and “metabolic syndrome”).^{8–10} Adiposopathy (or “sick fat”) is defined as adipocyte and adipose tissue dysfunction that contributes to metabolic disease. Table 1 outlines the causes of adiposopathy, as well as its anatomic, pathophysiologic, and clinical manifestations. As shown in Figure 2, positive caloric balance and sedentary lifestyle in genetically and environmentally susceptible patients often result in adipocyte hypertrophy and visceral fat accumulation, especially among those with impaired adipogenesis in the peripheral subcutaneous adipose tissue depots. Excessive adipocyte hypertrophy causes organellar dysfunction (especially of the mitochondria and endoplasmic reticulum), hormone dysregulation, impaired storage of fatty acids, increased circulating free fatty acids, and lipotoxicity to nonadipose tissue organs such as liver, muscle, and possibly pancreas. In addition, a positive caloric balance in individuals with inadequate adipogenesis in peripheral subcutaneous adipose tissue may also contribute to increased free fatty acid delivery to nonadipose tissue organs, as well as to increased energy storage and fat accumulation in visceral, pericardial, and perivascular fat depots. Impaired angiogenesis may precipitate hypoxia and subsequent immunopathic responses if adipocytes and adipose tissue growth exceeds vascular supply.

Thus, along with hormonal dysfunction, adiposopathy is associated with increased production of reactive oxygen species, oxidative stress, proinflammatory responses (eg, increased tumor necrosis factor alpha [TNF- α], interleukin-6 [IL-6], and C-reactive protein [CRP]), and decreased anti-inflammatory responses (eg, decreased adiponectin). Depending upon the subsequent crosstalk and interaction with other body tissues (such as muscle, liver, pancreas, etc.), the pathogenic endocrine and proinflammatory consequences of adiposopathy may directly contribute to atherosclerosis by pathogenic pericardial and/or perivascular effects or indirectly contribute to atherosclerosis by promoting or worsening metabolic diseases such as T2DM, high blood pressure, or dyslipidemia; all major risk factors of CVD.

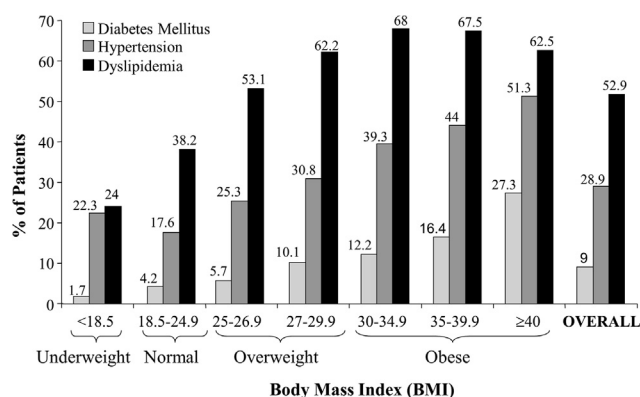


Figure 1 Relationship of BMI to prevalence of metabolic diseases derived from the National Health and Nutrition Examination Survey (1999–2002). The following definitions are used: (1) diabetes mellitus = diagnosed and previously undiagnosed type 1 or type 2 diabetes mellitus; (2) hypertension = administration of antihypertensive medication or systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg; and (3) dyslipidemia = at least one of the following: total cholesterol ≥ 240 mg/dL, TGs ≥ 200 mg/dL, LDL cholesterol ≥ 160 mg/dL, or HDL cholesterol < 40 mg/dL. Figure reproduced with permission.¹

Table 1 Adiposopathy (“sick fat”): summary of causality and examples of anatomic, pathophysiological, and clinical manifestations*

Causes of adiposopathy
Positive caloric balance
Sedentary lifestyle
Genetic predisposition
Environmental causes
Anatomic manifestations of adiposopathy
Adipocyte hypertrophy
Visceral, pericardial, perivascular, and other periorgan adiposity
Growth of adipose tissue beyond its vascular supply
Increased number of adipose tissue immune cells
“Ectopic fat deposition” in other body organs
Pathophysiological manifestations of adiposopathy
Impaired adipogenesis
Pathological adipocyte organelle dysfunction
Increased circulating free fatty acids
Pathogenic adipose tissue endocrine responses
(eg, increased leptin, increased TNF- α , decreased adiponectin, and increased mineralocorticoids)
Pathogenic adipose tissue immune responses
(eg, increased proinflammatory responses through increased TNF- α and decreased anti-inflammatory responses through decreased adiponectin)
Pathogenic interactions or pathogenic crosstalk with other body organs
(eg, liver, muscle, and central nervous system)
Clinical manifestations of adiposopathy
Hyperglycemia
High blood pressure
Elevated VLDL triglycerides and apo B (small dense LDL)
Low HDL-C
Metabolic syndrome
Atherosclerosis
Fatty liver
Hyperandrogenemia in women
Hypoandrogenemia in men
Cancer

HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; TNF- α , tumor necrosis factor alpha; VLDL, very-low-density lipoprotein.

*Adiposity can result in both fat-mass pathology and fat dysfunctional abnormalities resulting in adiposopathy. Reproduced with permission.⁶

Adipocyte and adipose tissue factors contributing to dyslipidemia

Adipose tissue is an active endocrine (Table 2) and immune (Table 3) organ.^{11,12} Among the more clinically relevant adipocyte hormones applicable to lipid metabolism are those responsible for triglyceride (TG) storage and free fatty acid release.^{12,13} Fat-containing adipocytes constitute most of adipose tissue volume, and adipocytes typically constitute the majority of adipose tissue cellular content. When adipocyte hypertrophy and adipose tissue becomes overly expansive, then this may result in adipocyte and adipose

tissue endocrine and immune dysfunction which promotes metabolic disease, including dyslipidemia (Table 4). Dyslipidemia is central to the adverse clinical consequences of adipocyte and adipose tissue dysfunction.¹⁴

In addition to adipocytes, adipose tissue also includes fibrous connective tissue, collagen, nerve cells, blood vessels, mesenchymal cells, fibroblasts, preadipocytes, endothelial precursor cells, smooth muscle cells, blood cells, and immune cells. Both adipocytes and adipose tissue-associated macrophages produce inflammatory factors. An increase in body fat increases the generation, accumulation, and activity of adipose tissue associated macrophages. Adipose tissue macrophages may be responsible for almost all adipose tissue TNF- α expression and significant amounts of other inflammatory factors.¹²

Perhaps the most well-described immunologic bioactive proteins secreted from adipocytes and adipose tissue are adipokines, which are secretory factors that include classic cytokines, complement factors, enzymes, growth factors, hormones, and matrix proteins. An increase in body fat often increases the secretion of proinflammatory adipokines by both adipocytes and adipose tissue-associated macrophages. Secretion of anti-inflammatory adipokines may be decreased, or at least relatively decreased, when overweight individuals with metabolic disease are compared to overweight individuals without metabolic disease. The net effect on increased proinflammatory adiposopathic responses and decreased anti-inflammatory adiposopathic responses is the onset or worsening of metabolic disease, including dyslipidemia and atherosclerosis. Table 4 describes some illustrative adipocyte and adipose tissue endocrine and immune factors involved in lipid metabolism. Among the potentially immunogenic adipocyte and adipose tissue factors are the proinflammatory hormone, leptin, and the anti-inflammatory hormone adiponectin, both of which potentially promote metabolic health, and/or metabolic disease, depending upon their direct cytologic function and/or dysfunction (Table 3 and 4). Finally, adipose tissue may also produce immunogenic factors that may directly contribute to inflammation (eg, via periorgan and perivascular effects) and indirectly influence inflammation via cross-talk and signaling to other body organs. For example, adiposopathy is associated with an increase in adipose tissue IL-6 release, causing increased hepatic secretion of CRP. This helps account for the increase in CRP levels often found in overweight patients, which is associated with increased CVD risk.⁶

Adipose tissue distribution and “adiposopathic dyslipidemia”

During positive caloric balance, individuals with genetic or environmental predisposition may have impaired adipogenesis (ie, impaired proliferation and/or differentiation) in peripheral subcutaneous adipose tissue. Through limiting energy storage in this adipose tissue depot, free fatty acids are increased in the circulation. An increase in free fatty acid delivery to other fat depots may increase their

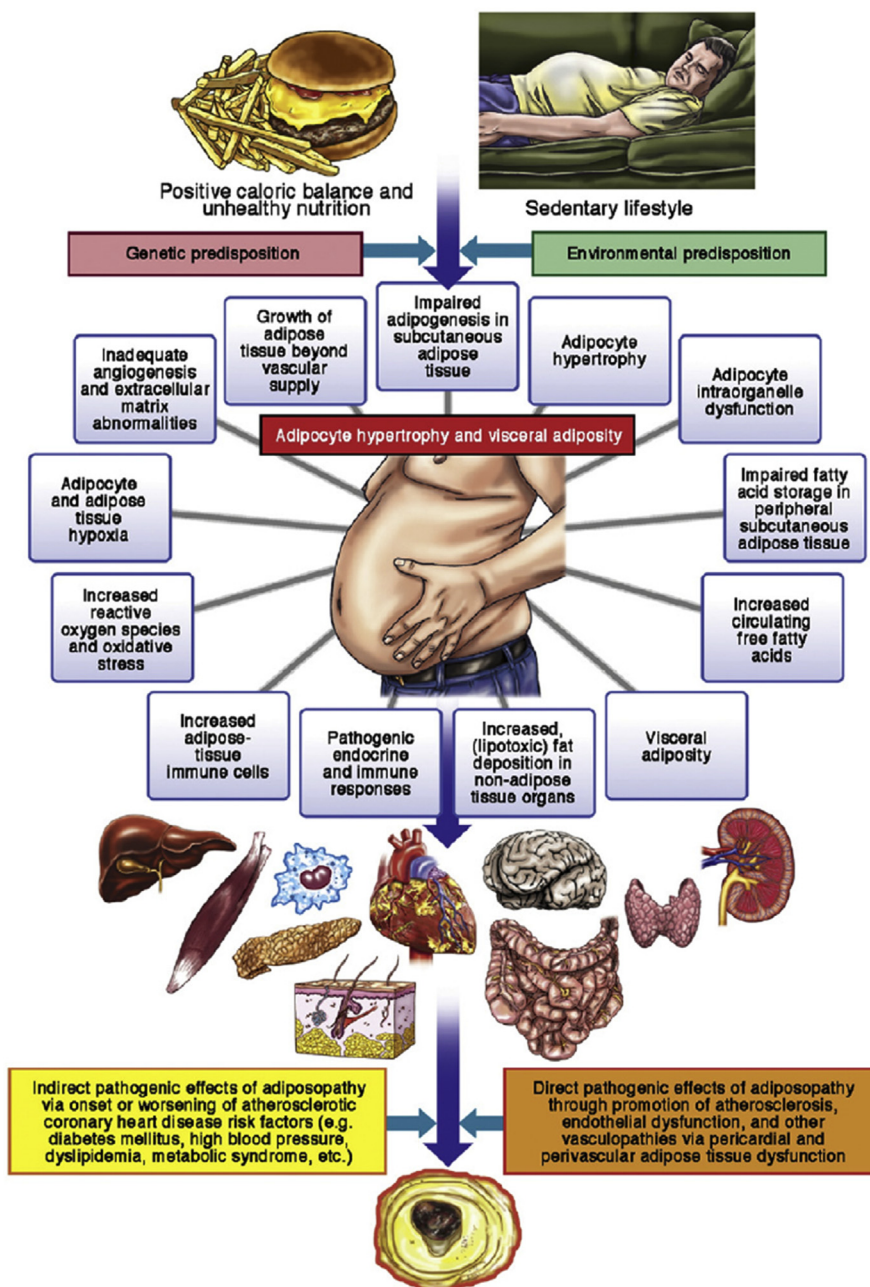


Figure 2 Adiposopathy: simplified relationship between pathogenic adipose tissue and cardiovascular disease. Adiposopathy is promoted by unhealthy nutrition and a sedentary lifestyle in genetically and environmentally predisposed individuals. With impaired adipogenesis of peripheral, subcutaneous adipose tissue during positive caloric balance, existing fat cells may hypertrophy, circulating free fatty acids may increase, and lipids may be deposited in nonadipose tissue organs (eg, liver, muscle, possibly pancreas) resulting in lipotoxicity. Adiposopathic endocrine and immune responses may be directly pathogenic to the cardiovascular system or otherwise interact with other body systems. If not mitigated by these other body organs, adiposopathy may indirectly cause or promote major atherosclerotic risk factors (type 2 diabetes mellitus, high blood pressure, or dyslipidemia). Figure illustration by Craig Skaggs; reproduced with permission.⁶

accumulation. Thus, an increase in visceral, pericardial, and perivascular adiposity might be considered a surrogate marker for the pathological impairment of energy storage in peripheral subcutaneous adipose tissue.¹⁵ Increased free fatty acid delivery to nonadipose tissues such as the liver may contribute to hepatosteatosis (fatty liver), which may also be considered an indicator of impaired energy storage in subcutaneous adipose tissue. Accordingly, fatty liver is a common clinical finding among overweight patients,

especially those with other adiposopathic-related metabolic abnormalities such as T2DM, high blood pressure, and dyslipidemia. From a lipid standpoint, increased free fatty acid delivery to the liver often increases hepatic secretion and TG enrichment of very-low-density lipoprotein (VLDL), which is clinically manifested by elevated fasting TG levels. Once in the circulation, hepatically derived VLDL particles undergo enzymatic exchanges with other lipoprotein particles such as high-density lipoproteins (HDL) and

Table 2 Adipose tissue as an endocrine organ: adipocytes and adipose tissue produce factors involved in metabolic processes important for human health*

Angiogenesis
Adipogenesis
Extracellular matrix dissolution and reformation
Lipogenesis
Growth factor production
Glucose metabolism
Production of factors associated with the renin-angiotensin system
Lipid metabolism
Enzyme production
Hormone production
Steroid metabolism
Immune response
Hemostasis
Element bindings
Adipose tissue has 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, catecholamine receptors, and other receptors.

*Disruption of adipose tissue endocrine function may contribute to metabolic disease. Reproduced with permission.⁶

low-density lipoproteins (LDL), via cholesteryl ester transfer protein (CETP) (Fig. 3). Once these TG-rich lipoprotein particles are subjected to various lipases, then the HDL particles may become smaller and more apt to undergo metabolism and excretion by the kidney, resulting in low HDL cholesterol (HDL-C) levels. Similarly, when TG-rich LDL particles interact with lipases, they may also become smaller and denser. The VLDL particles may undergo further lipolysis, resulting in VLDL remnants, which are also atherogenic. This adiposopathic dyslipidemic pattern is distinctly characteristic of the abnormal lipid levels found with pathogenic adipocyte and adipose tissue dysfunction and contrasts with other atherogenic dyslipidemias such as isolated severe hypercholesterolemia, which is often the result of genetic disturbances.

Lipids and insulin resistance

The association between adiposity and insulin resistance has been appreciated for decades. Randle et al¹⁶ first postulated a mechanism whereby lipids may impair insulin-stimulated glucose oxidation in muscle. In their “glucose-fatty acid cycle,” increased delivery and oxidation of lipids would promote accumulation of intracellular metabolites (eg, acetyl coenzyme A [CoA], nicotine adenine dinucleotide hydrogen) that would inhibit pyruvate dehydrogenase. This in turn would lead to the accumulation of glycolytic intermediates that would further impair glucose consumption (eg, glucose 6-phosphate [G-6-P]) inhibit hexokinase and presumably impair glucose uptake. Thus, in

Table 3 Adipose tissue as an immune organ: adipocytes and adipose tissue produce factors actively involved in immunological processes important for human health*

Proinflammatory adipose tissue factors
Factors with cytokine activity:
Adipsin, IL-1 β , IL-6, IL-8, IL-17D, IL-18, leptin, MCSF-1, MCP-1, MMIF, resistin, TNF- α , RANTES, and VASPIN
Acute-phase response proteins:
AGP, ceruloplasmin, CRP, haptoglobin, IL-1RA, lipocalins, metallothionein, pentraxin-3, PAI-1, and serum amyloid A
Proteins of the alternative complement system:
Adipsin, ASP, complement C3 and B
Chemotactic/chemoattractants for immune cells:
Eotaxin, interferon inducible protein, MCSF-1, MCP-1, MMIF, RANTES, resistin, stromal-derived factor 1, VAP-1, and VCAM-1
Eicosanoids/prostaglandins such as prostaglandin E ₂
Anti-inflammatory adipose tissue factors
Adiponectin
Annexin-1
IL-6 and IL-10
Transforming growth factor- β
Bone morphogenic factor
Nitric oxide
IL-1 receptor antagonist

AGP, alpha-1 acid glycoprotein; ASP, acylation-stimulating protein; CRP, C-reactive protein; IL, interleukin; MCP, monocyte chemoattractant protein; MCSF, macrophage colony-stimulating factor; MMIF, macrophage migration inhibitory factor; PAI, plasminogen activator inhibitor; RANTES, regulated on activation, normal T-cell expressed and secreted; TNF- α , tumor necrosis factor-alpha; VAP, vascular adhesion protein; VASPIN, visceral adipose tissue-derived serpin; VCAM, vascular cell adhesion molecule.

*Adipose inflammatory factors are produced by adipocytes and adipose tissue-associated macrophages. An increase in adipose tissue inflammatory response and a decrease in anti-inflammatory response may contribute to metabolic disease. Reproduced with permission.⁶

their model, the availability of lipids as a fuel source generated metabolic signals that impaired glucose oxidation by essentially inhibiting key glycolytic enzymes.

Although this may hold true for acute experimental conditions, it does not explain insulin resistance in chronic disease states, in which there are reductions in *both* insulin-stimulated oxidative and nonoxidative (ie, glycogen synthesis) muscle glucose use.¹⁷ In a series of studies, ¹³C and ³¹P magnetic resonance spectroscopy was used to noninvasively measure insulin-stimulated changes in muscle glycogen and intra-myocellular G-6-P in both patients with T2DM and in patients without T2DM but with first-degree relatives with T2DM.¹⁷⁻¹⁹ The rate of glucose and insulin-stimulated muscle glycogen synthesis was more than 50% lower in the T2DM subjects than in the control subjects¹⁷ and associated with lower muscle G-6-P concentrations.¹⁹ Subsequent in vivo measurements of intramyocellular glucose and G-6-P concentrations in insulin-resistant T2DM subjects is attributable primarily to a reduction in insulin-stimulated glucose transport activity caused by decreased insulin signaling.²⁰⁻²³ Studies demonstrating that impairments in

insulin signaling decreased glucose transport protein 4 (GLUT4) translocation and cell surface expression provided the molecular basis for the decreases in insulin-stimulated glucose transport.^{24,25}

Lipid-induced skeletal muscle insulin resistance

The coordinated intracellular response to insulin requires an intricate relay of signals. In skeletal muscle, insulin binds to its receptor, activating tyrosine kinase with subsequent phosphorylation and activation of insulin receptor substrate-1 (IRS-1; Fig. 5). When phosphorylated, IRS-1 activates 1-phosphatidylinositol 3-kinase (PI-3K), which, through signaling intermediaries, activates serine/threonine kinase 2 (Akt2), a serine/threonine-specific protein kinase also known as protein kinase B. Akt2 phosphorylates and inactivates AS160, a widely expressed protein that prevents GLUT4 translocation via its interaction with Rab proteins, a family of proteins primarily involved in vesicle trafficking.²⁶ Thus, insulin promotes the docking and fusion of GLUT4-containing vesicles to the plasma membrane. The tyrosine phosphorylation of IRS-1 and associated PI-3K activation were found to be impaired in insulin resistance rodent models.^{27,28} Similarly, IRS-1-associated PI-3K activity was significantly reduced in the muscles of human subjects undergoing the lipid infusions previously described, indicating that the lipid-induced reduction in insulin stimulated glucose transport was attributable to a defect in insulin signaling.²¹ A key question arises: what connects muscle lipid to impaired muscle insulin action? Is it the circulating plasma lipids or the lipids accumulating within insulin responsive tissues that are responsible?

Studies in normal weight adults without T2DM found that intramyocellular TG content is a far stronger predictor of muscle insulin resistance than circulating fatty acids,²⁹ suggesting that intramyocellular lipid and not plasma lipid concentration best relates to muscle insulin resistance. This empiric observation has been tested experimentally in normal rats infused with Intralipid (Sigma-Aldrich, St. Louis, MO) plus heparin. Although plasma fatty acids are acutely increased, muscle insulin resistance did not develop until 3–4 hours into the lipid infusion, concordant with the accumulation of intramyocellular diacylglycerol (DAG), and impairment in insulin signaling and muscle glucose uptake. Notably, insulin resistance occurred independently of changes in muscle TG content, thus dissociating muscle TG concentrations *per se* from insulin resistance.^{21,30}

DAGs are signaling intermediates that activate members of the protein kinase C (PKC) family. In these experiments, muscle lipid accumulation is associated with activation of the novel PKC (nPKC) isoform PKC θ , providing a potential link between lipid accumulation and alteration in intracellular signaling. This link between DAG-mediated activation of PKC and muscle insulin resistance has been replicated in human studies.^{31,32} Together, these studies support the paradigm that DAG accumulation in muscle

can lead to muscle insulin resistance through activation of nPKCs (Fig. 5).

Genetic mouse models have supported the role of DAG mediated activation of PKC θ as a mechanism for the development of insulin resistance. As an example, promoting lipid entry into muscle with muscle-specific overexpression of lipoprotein lipase (LPL) promotes muscle insulin resistance.³³ In contrast, preventing muscle lipid entry by deletion of LPL,³⁴ or other proteins involved in fat transport such as CD36^{35,36} or fatty acid transport protein 1,³⁷ prevents muscle lipid accumulation and protects against insulin resistance. Increasing energy expenditure also protects against lipid accumulation, as in mice overexpressing muscle-specific uncoupling protein-3³⁸ or deficiency of acetyl CoA carboxylase-2.³⁹ Hoehn et al⁴⁰ recently describe a different acetyl CoA carboxylase-2 knockout mouse strain that had similar rates of energy expenditure as wild-type mice, gained similar amounts of weight when placed on a high-fat diet and became insulin resistant, despite higher rates of fat oxidation. Taken together these data suggest that simply shifting substrate preference, without increasing total energy expenditure, will not protect against fat-induced insulin resistance.

Lipid-induced hepatic insulin resistance

In the liver, insulin activates the insulin receptor kinase, which phosphorylates IRS-1 and -2, which in turn activates PI-3K and ultimately Akt2 (Fig. 6).⁴¹ At this point, Akt2 activation promotes glycogen synthesis and inhibits gluconeogenesis. The mechanisms underlying the development of hepatic insulin resistance were studied in rats fed a high-fat diet for three days, an intervention that specifically leads to hepatic steatosis. This is associated with hepatic insulin resistance, without any significant change in muscle lipid content or peripheral insulin action.⁴² If mitochondrial fatty acid oxidation is increased, as with low doses of the mitochondrial uncoupler, 2,4-dinitrophenol, rats were protected from fat-induced hepatic steatosis and hepatic insulin resistance.⁴² In this model, hepatic steatosis was associated with proximal defects in insulin signaling with decreased tyrosine phosphorylation of IRS-1 and IRS-2 by the insulin receptor, ultimately impairing the ability of insulin to activate hepatic glycogen synthesis. This defect in insulin stimulated hepatic glycogen synthesis is similar to what has been demonstrated in patients with T2DM.^{43,44} PKCs again were the logical candidates to link hepatic steatosis and hepatic insulin resistance. Although PKC θ is poorly expressed in the liver, PKC ϵ , another nPKC (Fig. 6) is highly expressed and activated in the setting of fatty liver. If hepatic steatosis was prevented with the use of 2,4-dinitrophenol, PKC ϵ activation also was prevented. The association between PKC ϵ and hepatic insulin resistance has now been demonstrated in multiple other rodent models.^{39,45–48}

The specific role of PKC ϵ in the pathogenesis of hepatic insulin resistance was assessed using antisense

Table 4 Examples of Endocrine and Immune Adipocyte and Adipose Tissue Factors as Potential Contributors to “Adiposopathic Dyslipidemia.”^{12,295}

Adipocyte/adipose tissue factors	Association with adipocyte/adipose tissue excess	Mechanisms relative to lipid metabolism and potential contribution to adiposopathic dyslipidemia
Endocrine factors		
Lipid metabolism proteins/enzymes/hormones		
11 beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1)	11β-HSD1 is an enzyme produced in adipocytes (as well as other body tissues) that increases the conversion of inactive circulating cortisone to active cortisol. Expression of 11β-HSD1 at the adipocyte level may increase with excessive body fat.	Increased local 11β-HSD1 activity may contribute to dyslipidemia through glucocorticoid-enhanced lipolysis and decreased lipoprotein lipase (LPL) activity in peripheral, subcutaneous adipose tissue resulting in net increased free fatty acid release. ²⁹⁶ Increased 11β-HSD1 activity in visceral adipose tissue correlates to dyslipidemia (as well as hyperinsulinemia and hypertriglyceridemia). ²⁹⁷
Acylation-stimulating protein (ASP)	ASP is a lipogenic protein produced by adipocytes which is generated from cleavage of complement C3 via interaction with factor B and factor D (adipsin). ASP stimulates enzymes relative to the uptake of glucose for glycerol formation, and acylation of fatty acids, such as diacylglycerol acyltransferase, which is the terminal step in TG synthesis. ASP also increases pancreatic insulin secretion, increases LPL activity, and inhibits adipocyte hormone sensitive lipase activity. The net effect is short-term energy clearance through a reduction in circulating TG and free fatty acid levels, and an increase in intra-adipocyte postprandial TG synthesis and storage. ASP may be increased with excessive body fat.	If adiposopathy is present during positive caloric balance, then impaired and/or blunting of the increase in postprandial ASP levels and/or activity may result in inadequate energy clearance, increased free fatty acids, and dyslipidemia. ^{*,298} (See discussion of free fatty acids below.)
Adipocyte triglyceride lipase (ATGL)	ATGL is a key lipase enzyme found in adipocytes and other non-adipose cells, whose activity can be regulated by regulatory proteins such as perilipin (see below). Animal studies suggest ATGL and hormone sensitive lipase (see below) are responsible for more than 95% of triglyceride hydrolase activity in white adipose tissue. ATGL expression is reduced with obesity. ^{299,300}	Impairment of ATGL activity may reduce catecholamine stimulated lipolysis within adipocytes (see catecholamine receptor discussion below). ³⁰¹ The implications regarding the dyslipidemia found with adiposity are unclear. (See discussion of HSL below.)
Comparative gene identification-58 (CGI-58)	CGI-58 is a hydrolase protein which facilitates activation of ATGL. It is activated with β-adrenergic stimulation of adipocytes (see catecholamine receptors below). ³⁰¹ CGI-58 expression may not change with obesity. ³⁰⁰	The role of CGI-58 and the onset of dyslipidemia with adiposity are unclear. (See discussion of ATGL above, and HSL below.)
Glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein-1 (GPIHBP1)	GPIHBP1 is an endothelial cell surface glycoprotein required for the lipolytic processing of triglyceride rich lipoproteins and moving lipoprotein lipase from interstitial spaces to the capillary lumen, which is mainly regulated by peroxisome proliferator activated receptor (PPAR) gamma, which is the same nuclear receptor that helps regulate a number of processes involved in adipocyte proliferation and differentiation. ³⁰² In obese humans, its expression is decreased in visceral adipose tissue relative to subcutaneous adipose tissue. ^{301,303}	If positive caloric balance results in accumulation of visceral adipose tissue, then the presence of increased visceral adipose tissue endothelial cells may promote an inflammatory state with decreased expression of genes such as GPIHBP1. ^{301,303} If GPIHBP1 expression is absent (or presumably decreased), then lipoprotein lipase may be mislocalized to the interstitial spaces, leading to hypertriglyceridemia. ³⁰⁴

Hormone-sensitive lipase (HSL)

HSL is the principal regulator enzyme of intra-adipocyte lipolysis, having decreased expression with increased adiposity and hyperinsulinemia. Postprandial increases in insulin down-regulate HSL (and up-regulate LPL), decreasing intra-adipocyte TG lipolysis, increasing extra-adipocyte TG lipolysis, and increasing the net uptake and trapping of free fatty acids within adipocytes for TG storage. This lipogenic activity may increase adipocyte size, and if excessive, may contribute to the adipocyte hypertrophy characteristic of adiposopathy. Conversely, fasting decreases insulin levels, which activates adipocyte HSL (and down-regulates adipose tissue associated LPL), which increases net free fatty acid release from adipose tissue. HSL is down-regulated with increasing adiposity.

Reduced HSL activity decreases free fatty acid release from adipocytes, decreases free fatty acid delivery to the liver, decreases VLDL particle formation in the liver and reduces clearance of HDL particles. These represent favorable lipid effects. However, with adiposopathy, these favorable effects may be impaired, blunted or insufficient, thus contributing to dyslipidemia.* Furthermore, reduced activity of HSL may not be sufficient to overcome other lipolytic effects associated with adiposopathy, such as increased lipolytic contributions of increased β -adrenergic activity, impaired insulin activity at the level of the adipocyte, and the effects of perilipin (described below). Thus, despite decreased HSL activity with adiposity, adiposopathic responses may contribute to a net increase in circulating free fatty acids (described below), and thus may result in dyslipidemia.

Lipoprotein lipase (LPL)

LPL is an enzyme produced and secreted by adipose tissue, as well as other body tissues (e.g. muscle), which upon attachment to the luminal side of capillary blood vessels, interacts with TG-rich lipoproteins, and facilitates extra-adipocyte, intravascular TG lipolysis. Apolipoprotein CII facilitates LPL-mediated TG hydrolysis; apolipoprotein CIII inhibits LPL-mediated TG hydrolysis. Human adipocytes do not synthesize lipids, but instead rely upon LPL-mediated hydrolysis of circulating TG-rich lipoproteins. Normally, after feeding, 80% to 90% or more of free fatty acids are trapped by adipocytes as the result of the net effect of insulin, and enzymes such as LPL and hormone sensitive lipase. Thus, postprandial free fatty acids are much lower than fasting levels. LPL activity increases with excessive body fat.

During fasting, hydrolysis of circulating TGs most often occurs via interaction of LPL with VLDL particles. After meals, LPL substantially interacts with chylomicrons. Postprandial increases in insulin up-regulate adipocyte LPL, allowing for concentration-dependent passive adipocyte fatty acid uptake, as well as active fatty acid uptake (such as through fatty acid transport protein, described below). Insulin also down-regulates hormone sensitive lipase, which decreases intra-adipocyte TG lipolysis, further facilitating the efficient trapping of fatty acids within adipocytes. TG levels are thus reduced; lipogenesis and adipocyte size are increased. In patients with adiposopathy, the relative activity and effect of LPL and hormone sensitive lipase may be reduced or insufficient, impairing lipolysis, impairing post-prandial free fatty acid clearance, and thus increasing TG levels.* (See free fatty acid discussion below.) Therapeutically, PPAR- α agonists (fibrates) and omega-3 fatty acids increase LPL as a major component of their mechanism of action towards reducing TG levels.²⁶⁰

(continued on next page)

Table 4 (continued)

Adipocyte/adipose tissue factors	Association with adipocyte/adipose tissue excess	Mechanisms relative to lipid metabolism and potential contribution to adiposopathic dyslipidemia
Perilipin	Perilipin is an intra-adipocyte regulatory protein that coats lipid-storage droplets. Basal perilipin inhibits and/or protects against the lipolytic activity of hormone sensitive lipase. During stimulated lipolysis, phosphorylated perilipin may increase the catalytic activity of hormone sensitive lipase. ³⁰⁵ Perilipin may be increased with adiposity.	If fat cells hypertrophy with adiposity, then the relative decrease in surface perilipin may expose adipocytes to greater TG breakdown by hormone sensitive lipase, increasing net fatty acid release from adipocytes, resulting in dyslipidemia (see the discussion of free fatty acids below). Additionally, adipocyte hypertrophy may cause adiposopathic organelle dysfunction (Figure 2; Table 1) (such as mitochondrial dysfunction) and endoplasmic reticulum stress, which may increase phosphorylation of perilipin, increase intra-adipocyte lipolysis, worsen dyslipidemia, and contribute to lipotoxicity of other body organs such as liver, muscle and possibly pancreas. ³⁰⁶ (See Figure 4)
Sterol regulatory element binding proteins (SREBPs)	SREBPs are transcription factors found in adipocytes and other body tissues that regulate intracellular levels of lipids, such as up-regulating or down-regulating enzymes relative to cholesterol synthesis. SREBP expression is decreased with excessive body fat and increased with insulin (whose level is often increased with excessive body fat).	Reduced lipogenesis in adipocytes via adiposopathy-induced reduction in SREBP activity could potentially result in energy overflow in the form of free fatty acids to other body tissues, resulting in lipotoxicity and dyslipidemia (see discussion of free fatty acids below). An increase in TNF- α (see below) often occurs with obese states, and may further decrease SREBP activity. ³⁰⁷
Lipids and apolipoproteins		
Free fatty acids (FFA)	Free fatty acids are unesterified, circulating, carbon chain carboxylic acid anions that are termed “free” because they do not share electrons with other substances (i.e. are not covalently linked). Less than 1% of free fatty acids are actually free in solution, with most being ionically bound to and complexed to plasma proteins (i.e. albumin). FFAs undergo transport across adipocyte membranes via transport proteins, and possibly gradient-dependent diffusion. If storage in peripheral subcutaneous adipose tissue is impaired, as occurs with excessive body fat resulting in adiposopathy, then circulating FFA levels may increase, increasing delivery to other fat depots contributing to visceral and perivascular adiposity.	In addition to contributing to visceral and perivascular adiposity, chronically elevated circulating FFA may contribute to lipotoxicity to liver, muscle, and possibly pancreas, often resulting in hepatosteatosis, insulin resistance in tissues such as liver and muscle), and a possible decrease in pancreatic β -cell insulin secretion. The increased delivery of FFA to the liver may increase VLDL secretion, thus contributing to hypertriglyceridemia, reduced low HDL-C levels, increased smaller / more dense LDL particles, and increased lipoprotein remnants. (See Figure 3)
Apolipoprotein (apo) A1	Apo A1 promotes cholesterol efflux from many body tissues. ³⁰⁸ Apo A1 is the main protein constituent of HDL particles, and activates lecithin-cholesterol acyltransferase, esterifying cholesterol, and thus allowing for greater cholesterol delivery to and removal by the liver.	Apo A1 may increase energy expenditure and uncoupling protein 1 expression in brown adipose tissue. ³⁰⁹ Apo A1 in HDL particles promotes cholesterol efflux from adipocytes. ³¹⁰

Apolipoprotein (apo) C1	Apo C1 is expressed in adipose tissue (as well as other tissues such as liver), and is found on TG rich lipoproteins and HDL. Apo C1 activates lecithin-cholesterol acyltransferase, esterifying cholesterol, and thus allowing for greater cholesterol delivery to and removal by the liver.	Overexpression of apo C1 results in inhibition of VLDL uptake by hepatic receptors, and diminished net uptake of free fatty acids in adipose tissue resulting in decreased adipose tissue mass, increased total cholesterol levels, increased TG levels and hepatic steatosis. ³¹¹
Apolipoprotein (apo) D	Apo D belongs to the lipocalin family, and is expressed in adipose tissue, as well as central nervous system, sex organs, and other body tissues. Apo D may bind and help transport small molecules such as cholesterol, sex hormones, bilirubin, and arachidonic acid. Apo D is also found on HDL particles may form a complex lecithin-cholesterol acyltransferase.	In adipocytes, apo D may have a role in cholesterol efflux. ¹⁴ Apo D may covalently link with apo A-II, and may also be present on VLDL and LDL. Apo D mutations are associated with elevated TG and decreased HDL levels. ³¹²
Apolipoprotein (apo) E	Apo E is found in adipocytes, and facilitates adipocyte TG accumulation and cholesterol efflux to HDL particles. Apo E expression decreases with positive caloric balance, and increases with weight loss. ³¹³ Apo E is also preset on TG-rich lipoproteins.	Lipid effects of increased apo E expression might be illustrated by PPAR- γ stimulation, which may increase adipocyte apo E gene transcription mediated by liver receptor x pathways, ³¹⁴ which in turn may decrease TG blood levels, and increase HDL-C levels. Lipoprotein associated apo E assists with lipoprotein binding to liver and peripheral cells.
Transfer proteins		
Cholesteryl ester-transfer protein (CETP)	CETP is a transfer enzyme. Adipocyte expression of CETP contributes to circulating CETP levels. CETP facilitates exchanges of TGs and cholesterol between lipoproteins. CETP is increased with cholesterol feeding and body weight.	Adiposity may increase CETP activity which may decrease HDL-C, and increase atherogenic lipoprotein cholesterol, such as increased VLDL-C, IDL-C, and LDL-C. Increased CETP activity may also decrease LDL particle size. Weight loss in overweight patients may decrease CETP levels and thus improve many of the dyslipidemias associated with the adiposopathy-induced increase in CETP. ³¹⁵
Phospholipid transfer protein (PTP)	PTP is a transfer enzyme produced by adipose tissue and other body tissues that catalyzes the exchange of phospholipids from TG-rich lipoproteins to HDL particles. PTP synthesis and activity are increased with excessive body fat.	An increase in the transfer of phospholipid into HDL particles results in the formation of larger, less dense HDL particles. The net effect of increased PTP on HDL functionality, peripheral cholesterol transport, and atherosclerosis is unclear. ³¹⁶
Biologic transporters		
Adenosine triphosphate (ATP) binding cassette transports (ABC transporters)	ABCA1 is a membrane-associated cholesterol transporter expressed in many tissues, including adipose tissue; adipose tissue is the body's largest reservoir of free cholesterol.	Adipose tissue ABCA1-dependent cholesterol efflux and nascent HDL particle formation contributes to HDL biosynthesis. ³¹⁷ Genetic reduction of ABCA1 causes familial alpha-lipoprotein deficiency (Tangier disease) characterized by low HDL-C, high TG levels, premature atherosclerosis, hepatosplenomegaly, orange/yellow tonsils, clouding of the cornea, and neuropathy.

(continued on next page)

Table 4 (continued)

Adipocyte/adipose tissue factors	Association with adipocyte/adipose tissue excess	Mechanisms relative to lipid metabolism and potential contribution to adiposopathic dyslipidemia
Fatty acid transport protein (FATP)	FATP are a family of membrane proteins produced by adipocytes (and skeletal muscle) which transport fatty acids (enhancing adipocyte uptake) and which have acyl-CoA synthetase activity and thus activate the fatty acids in preparation for adipocyte TG formation and storage. FATP expression is increased by insulin.	Impairment of FATP inhibits fatty acid uptake into adipocytes, which increases the risk of lipotoxicity and dyslipidemia (see discussion of free fatty acids above). Several phenothiazine drugs are known to inhibit FATP and produce adverse metabolic effects such as hypertriglyceridemia. Thus, inhibition of FATP may be a useful screening system to assess the impact of drugs on fatty acid uptake and dyslipidemia. ³¹⁸
Glucose transporter 4 (GLUT4)	GLUT4 is a glucose transporter found in adipocytes and muscle. GLUT4 facilitates lipogenesis in that glucose transport into adipocytes supplies acetyl-CoA for fatty acid synthesis. TGs are formed when fatty acids are combined with glycerol, which may also be derived from glucose. Insulin-induced GLUT4 translocation to the plasma membrane may be blunted in more adiposopathic large fat cells, versus more functional small fat cells, promoting adiposopathy, inhibiting insulin responsiveness, impairing energy storage, and potentially contributing to increased circulating free fatty acids. ³¹⁹	Adiposopathic increases in circulating free fatty acids due to blunted GLUT4 activity in hypertrophied fat cells may contribute to hepatosteatosis and adiposopathic dyslipidemia, characterized by increased TG, decreased HDL-C, and increased smaller/more dense LDL particles. Also, the increase in circulating free fatty acids may repress GLUT4 in non-adipose tissues, further contributing to total body insulin resistance. ³²⁰
Cellular receptors Low density lipoprotein receptors (LDL-Rs)	LDL-Rs facilitate the body tissue uptake of cholesterol from lipoproteins. LDL-Rs are found on adipocytes. The binding of LDL to LDLRs may be reduced with increased adiposity, ³²¹ and dietary cholesterol and saturated fat may down-regulate LDL-R activity as well.	After meals, reduced clearance of lipoproteins via LDL-Rs due to adiposity may contribute to delayed clearance of postprandial lipoprotein remnants, and thus contribute to postprandial dyslipidemia. ³²¹ During fasting, if LDL-R activity is sufficient, then LDL-C levels may not increase with increased adiposity. Nonetheless, the potential adverse consequences of adiposity and dietary cholesterol and saturated fats on LDL-R activity supports a nutritional plan incorporating appropriate calories, as well as low saturated fat and low cholesterol diet in dyslipidemic patients, such as those with familial hypercholesterolemia. ^{322,323}

Catecholamine receptors	<p>While parasympathetic stimulation is likely a minor contributor to anabolic lipogenesis, sympathetic stimulation is a major contributor to catabolic lipolysis. Autonomic nerve cells are present in adipose tissue and β-adrenergic receptors are found in adipocytes. Although catecholamine activity is increased with increased adiposity, excessive body fat impairs lipolysis in white adipocytes and impairs nonshivering thermogenesis in brown adipocytes.³²⁴ Increased HSL activity by β-adrenergic agonists in adipocytes involve binding of catecholamines to G protein coupled β-adrenergic receptors, which stimulates cyclic adenosine monophosphate (cAMP) levels, which activates protein kinase A, which phosphorylates perilipin-1 and HSL. The phosphorylation of perilipin-1 facilitates ATGL activation by CGI-58 and the translocation of phosphorylated and activated HSL from the cytoplasm to lipid droplets. Thus, these enzymes hydrolyze triglycerides from diglycerides to monoglycerides, which are then converted to glycerol and fatty acids by monoglyceride lipase.³⁰¹</p>	<p>With excessive body fat, the increase in adipose tissue noradrenergic activity may be blunted, which impairs the sympathetic nervous system capacity to counter adiposity through catabolic reductions in adipocyte size and increase energy expenditure.* Nonetheless, a net increase in lipolysis due to a net increase in adipose tissue sympathetic nervous system activity increases free fatty acid release, contributing to dyslipidemia. (See the discussion of free fatty acids above.) Not only do increased noradrenergic responses contribute to dyslipidemia, but adiposopathy-related increases in sympathetic nervous system activity may also contribute to associated high blood pressure through increased catecholamine responses via leptin, pro-opiomelanocortin and melanocortin 4 pathways.³²⁵</p>
Scavenger receptor class B type 1 (SR-B1)	<p>SR-BI are receptors that recognize LDL particles modified by oxidation or acetylation. SR-B1 receptors are expressed by tissues such as adipocytes.</p>	<p>Adipocyte SR-B1 may promote cholesterol transport from adipocytes to HDL,¹³² which might be expected to increase HDL-C levels.</p>
Fatty acid translocase (CD36)	<p>CD36 is a membrane glycoprotein found on the surface of adipocytes, platelets, monocytes/macrophages, endothelial, and smooth muscle cells. CD36 belongs to the scavenger receptor family involved in atherosclerosis, angiogenesis, lipid metabolism, glucose metabolism, inflammation (including induction of innate immunity to malaria infection), platelet biology, and taste. CD36 is up-regulated in peripheral subcutaneous adipose tissue when adiposity is associated with metabolic disease such as T2DM (i.e. reflective of adiposopathy).³²⁶</p>	<p>CD36 has undergone extensive study for its role as a vascular scavenger receptor for modified/oxidized LDL, macrophage lipid accumulation, and inflammatory responses. The net lipid effects of CD36 overexpression or deficiency are unclear. Some reports suggest adipose tissue CD36 expression promotes transport of fatty acids into adipocytes, contributing to adipocyte hypertrophy, with potential adipocyte apoptosis, which in turn, promotes macrophage infiltration, and adiposopathic immune responses (See Figure 2).³²⁷ Other reports suggest CD36 deficiency (due to specific polymorphisms) may protect against the metabolic syndrome, with increased HDL-C and decreased TG levels.³²⁸ Interestingly, expression of CD36 may enhance taste preference for fat consumption.³²⁹</p> <p style="text-align: right;"><i>(continued on next page)</i></p>

Table 4 (continued)

Adipocyte/adipose tissue factors	Association with adipocyte/adipose tissue excess	Mechanisms relative to lipid metabolism and potential contribution to adiposopathic dyslipidemia
Peroxisome proliferator activated receptor gamma (PPAR- γ)	PPAR- γ are nuclear receptors found in adipocytes for which fatty acids are the natural ligand. PPAR activity increases with overfeeding, ³³⁰ and PPAR- γ agonism promotes adipogenesis.	PPAR- γ agonism may increase energy (fatty acid) storage capacity through promoting adipocyte proliferation and differentiation, which increases insulin sensitivity, reduces hyperglycemia, and may increase HDL and increase LDL particle size. Thiazolidinediones are PPAR- γ therapeutic agents that “paradoxically” improve lipid and glucose levels (which are normally associated with too much fat), by adding more functional fat (adipogenesis). ^{6,302}
Immune factors		
Adiponectin	Adiponectin is an adipocyte hormone involved in glucose and lipid metabolism. Relative to other circulating adipocyte hormones, adiponectin concentrations are substantially higher. Adiponectin has immunologic properties, which help account for why it is often characterized as an adipokine / adipocytokine. Regarding atherosclerosis, adiponectin is considered anti-inflammatory; however, adiponectin may have pro-inflammatory activities with some chronic inflammatory and autoimmune diseases. ^{331,332} Adiponectin blood levels are decreased with increased adiposity and visceral fat, and increased with high dietary fiber and omega-3 fatty acids, as well as increased physical activity and hypocaloric diet in overweight patients. ³³³	Possibly related to adiponectin’s facilitation of insulin sensitivity, reduced adiponectin levels are associated with adiposopathic dyslipidemia (e.g. elevated TG, reduced HDL-C, and increased apolipoprotein B levels). Reduced adiponectin levels are also associated with decreased LPL activity, which may promote increased TG levels, and increased hepatic lipase activity, which may increase smaller, more dense LDL particles. Finally, reduced adiponectin levels are associated with fatty liver (hepatosteatosis). ¹⁴
Leptin	Leptin is an adipocyte-derived hormone involved in lipid metabolism, glucose metabolism, energy expenditure, and regulation of pro-inflammatory T lymphocyte and anti-inflammatory acute and innate immune responses. Leptin’s immunogenic properties help account for why it is often characterized as an adipokine/adipocytokine. ³³¹ Leptin levels are increased with excessive body fat.	The predominant effect of leptin activity on peripheral lipid metabolism is likely due to central nervous effects on nutritional intake and possibly energy expenditure. ³³⁴ Leptin may have local adipocyte effects, such as promoting lipolysis, stimulating fatty acid oxidation, and inhibiting lipogenesis (e.g. inhibiting sterol response element binding protein-1c, described above). ¹⁴ Administration of leptin to overweight patients with leptin-deficient lipodystrophy dramatically decreases body fat, decreases TG levels, and improves glycemic control. Administration of leptin and/or leptin analogues to overweight individuals with elevated leptin levels has little to modest metabolic effects, suggesting the leptin’s maximum activity is found at the upper range of normal. Additionally, overweight individuals may have the so called central nervous system “leptin resistance,” a condition exacerbated by high fat diet and hypertriglyceridemia, and improved by increased physical activity. ^{335,336}

C-reactive protein (CRP)	CRP is an acute phase reactant that is not only a surrogate marker of vascular inflammation, but may also directly contribute to atherosclerosis and thrombosis. ⁶ While CRP may be released from adipose tissue, it is likely that adiposopathic increases in CRP are mostly due to increased adipose tissue release of IL-6, which stimulates CRP production from the liver. Thus, CRP is generally increased with adiposity.	While little evidence supports CRP as directly worsening dyslipidemia, it is of interest that reduction in inflammatory markers such as CRP (and IL-6) with statins may in part be due to statin-induced reductions in adipose tissue inflammation. ⁶
Interleukin 6 (IL-6)	IL-6 is an adipokine produced by adipocytes and other body tissues that may increase β -adrenergic lipolysis as evidenced by increased isoproterenol-stimulated lipolysis. ³³⁷ Additionally, IL-6 may inhibit adipocyte adiponectin production, impair insulin signaling by down-regulation of insulin receptor substrate and up-regulate suppressor of cytokine signaling 3, which may contribute to insulin resistance. ¹⁴ While IL-6 is increased with increased fat cell size and increased fat mass, the adiposopathic increase in isoproterenol-stimulated lipolysis may be independent of adiposity and fat cell size. ³³⁷	IL-6 induced lipolysis and IL-6 induced insulin resistance would be expected to contribute to adiposopathic dyslipidemia (described previously). Also the increase in IL-6 production with adiposopathy is likely the predominant contributor to increase CRP found in overweight individuals. ⁶
Tumor necrosis factor (TNF)	TNF (also known as TNF- α or cachectin), is an adipokine produced by adipose tissue macrophages and other tissues. In adipose tissue, TNF promotes lipolysis, and impairs both adipogenesis and lipogenesis. In the hypothalamus, TNF decreases appetite, and stimulates the release of the catabolic corticotropin releasing hormone. In the liver, TNF increases the expression of genes involved in fatty acid synthesis, decreases genes involved with fatty acid oxidation. TNF may also increase hepatic insulin resistance by promoting serine-phosphorylation of insulin receptor substrate-1 which impairs insulin signaling, and may stimulate hepatic CRP secretion. Finally, TNF is a chemoattractant for immune cells, and enhances macrophage phagocytosis and macrophage inflammatory responses. TNF may be increased with excessive body fat.	TNF's promotion of adipocyte lipolysis and inhibition of adipogenesis may increase circulating free fatty acids, contributing to lipotoxicity and dyslipidemia (see discussion of free fatty acids above). TNF's increase in hepatic fatty acid synthesis and decrease in hepatic fatty acid oxidation increases VLDL secretion that, along with TNF's inhibition of LPL decreased adiponectin expression, and decreased insulin sensitivity, contributes to hypertriglyceridemia. Finally, increased TNF activity increases expression of other inflammatory factors (e.g. IL-1 and IL-6), all which may contribute to adiposopathic dyslipidemia. ¹⁴

*An absolute increase or decrease in an adipocyte and/or adipose tissue factor level associated with a metabolic disease such as dyslipidemia may not necessarily mean causality. Instead, it is a blunting of the absolute change in an adipocyte / adipose tissue factor which may represent a pathological response.

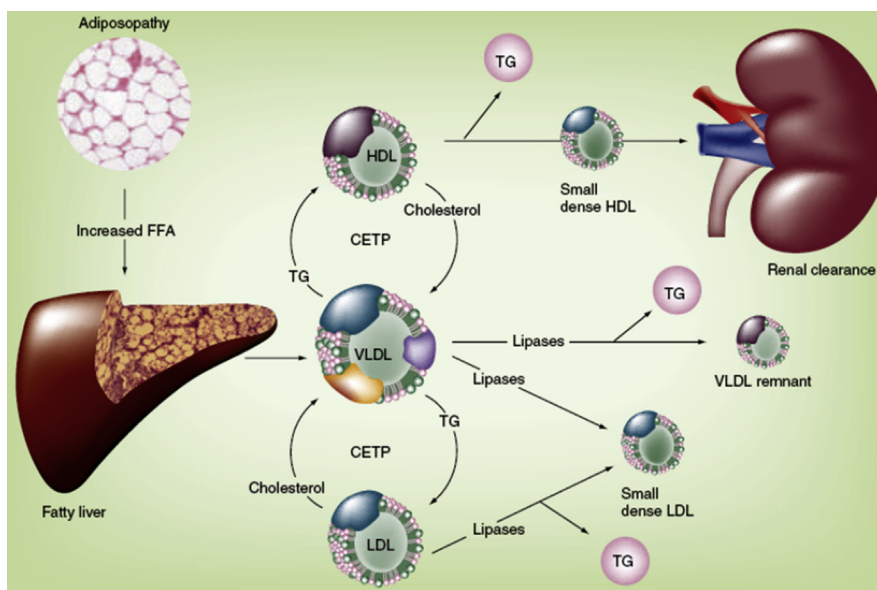


Figure 3 Adiposopathy in the fasting state and the contribution to the lipid pattern typically found with the metabolic syndrome. The presence of adiposopathy may result in increased fasting free fatty acid (FFA) release, contributing to fatty liver and increased VLDL particles, which carry TGs. Through metabolic processes involving cholesteryl ester-transfer protein (CETP), and various lipases, small dense HDL particles are created, which are more easily metabolized and cleared by the kidneys, and smaller LDL particles, which may be more atherogenic. The lipid pattern of hypertriglyceridemia, low HDL-C, small dense LDL particles, and increased lipoprotein remnants is a characteristic dyslipidemia often found in T2DM and metabolic syndrome. Figure reproduced with permission.²⁹⁵

oligonucleotides (ASOs) against PKC ϵ . ASOs are synthetic oligonucleotides modified with a 2'-O-(2-methoxy) ethyl modification and phosphorothioate bond to enhance potency, stability, and cell permeability.⁴⁹ They are taken up preferentially in liver, adipose tissue, and the kidney, although not in other key tissues such as muscle, brain, or pancreatic β cells. The effect of a specific ASO against

PKC ϵ was assessed in rats challenged with a 3-day high-fat diet. Although fat accumulation, and specifically DAG accumulation, was equal in all groups, the PKC ϵ ASO treatment improved hepatic insulin sensitivity and insulin signaling. The latter was associated with improved activation of the insulin receptor itself. Whereas high-fat feeding impaired insulin receptor kinase activation in comparison

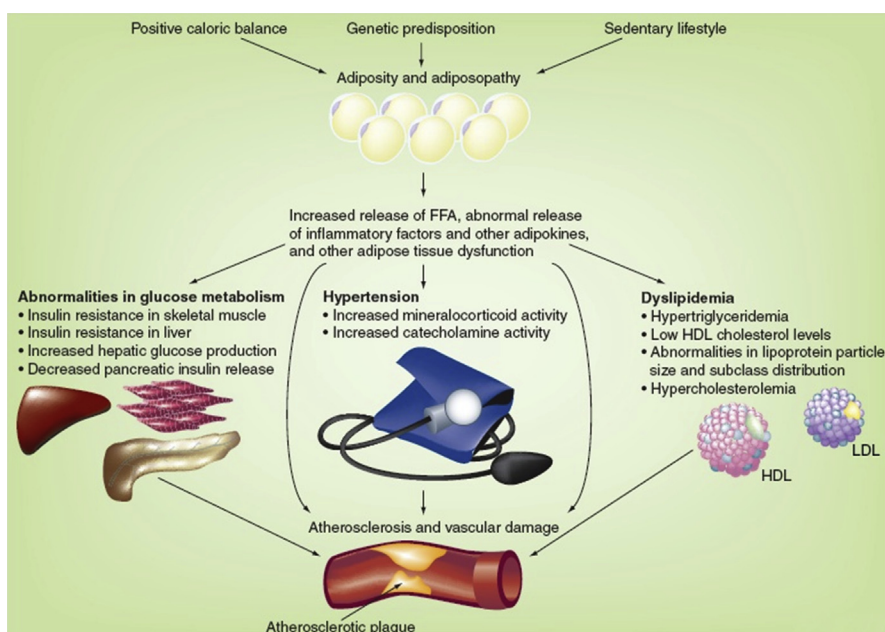


Figure 4 Inter-relationship between adiposopathy, type 2 diabetes mellitus, hypertension, dyslipidemia and atherosclerosis. Reproduced with permission.²⁹⁵ FFA, free fatty acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

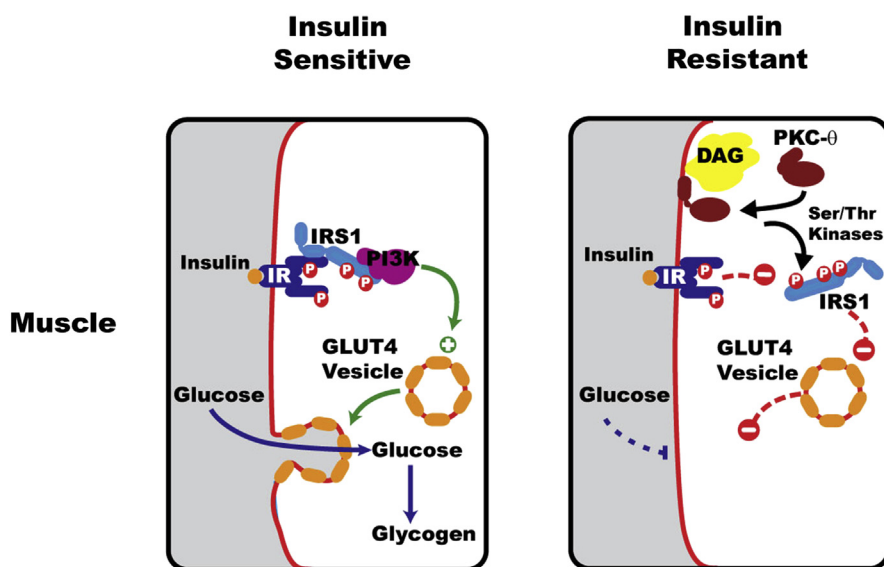


Figure 5 Mechanisms for insulin action and development of lipid induced insulin resistance in skeletal muscle. In the muscle, insulin acts to stimulate the translocation of glucose transporter type 4 (GLUT4) containing vesicles to the plasma membrane, allowing for glucose entry into the myocyte. In the insulin resistant state (right), accumulation of diacylglycerol (DAG) in the muscle activates protein kinase C theta (PKCθ), leads to serine phosphorylation of insulin receptor substrate-1 (IRS-1), and impairs GLUT4 translocation to the membrane.

with control-chow fed rats, insulin-stimulated kinase activation was preserved in high-fat fed rats treated with PKCε ASO. To summarize, with hepatic steatosis, DAG accumulation activates PKCε, which impairs insulin receptor activation, causing hepatic insulin resistance (Fig. 6).

The studies in rodent models are invaluable for understanding the potential cellular mechanisms for the pathogenesis of insulin resistance, but are these pathways relevant to humans? Recently, Kumashiro et al⁵⁰ studied a cohort of obese, non-T2DM subjects who were undergoing

bariatric surgery and assessed each of these pathways in flash-frozen liver biopsies. Hepatic DAG strongly correlated with insulin resistance as assessed by the homeostatic model of insulin resistance (HOMA-IR; much better so than BMI) and activation of PKCε. In contrast, other lipid metabolites (eg, total fatty acyl-CoA, ceramides, etc.) do not relate to insulin resistance. These data support the hypothesis that DAG-mediated activation of PKCε causes insulin resistance in humans with nonalcoholic fatty liver disease (NAFLD).

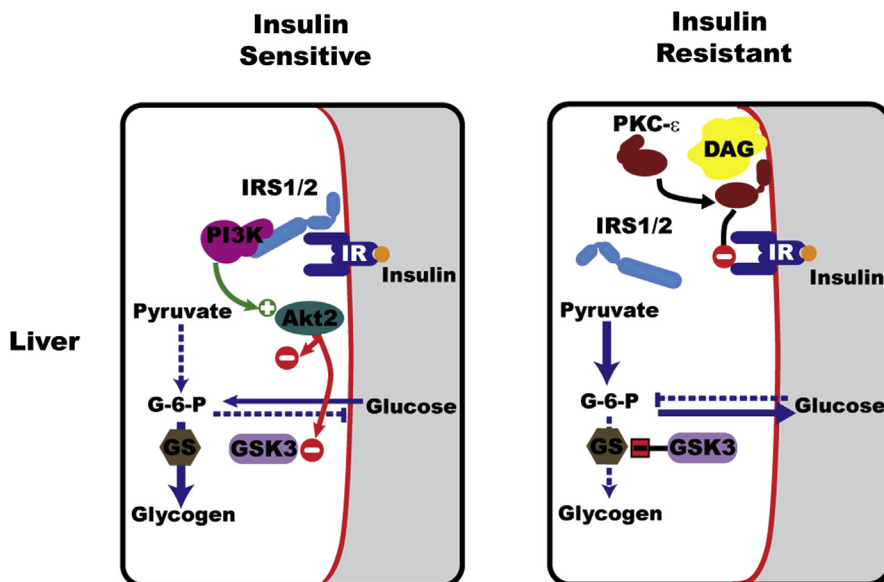


Figure 6 Mechanisms for insulin action and development of lipid-induced insulin resistance in the liver. In the insulin-sensitive liver (left), insulin inhibits gluconeogenesis and activates glycogen synthesis, thereby decreasing hepatic glucose production. In the insulin resistant state (right), DAG activates PKCε, leading to impaired insulin signaling and diminished regulation of hepatic glucose production. Akt2, serine-threonine kinase 2 (also known as protein kinase B) activation; GS, glycogen synthase; IR, insulin receptor.

Other hypotheses

In addition to DAG accumulation, other mechanisms for the genesis of insulin resistance have been proposed. Increases in plasma cytokines are associated with adiposity and thought to contribute to the development of insulin resistance, suggesting that activation of the innate immune system may play a role in the pathogenesis of insulin resistance. One common mechanism that has been proposed to explain this association is the cytokine mediated activation of the c-jun N-terminal kinase 1 (JNK1), which in turn may impair insulin signaling. Genetic manipulation of inflammatory pathways in rodents has offered some insights, but many of these models have subtle alterations in energy balance and tissue lipid accumulation that can contribute to the phenotype. For example, JNK1 knockout mice are protected from diet-induced insulin resistance and may suggest that blocking inflammatory pathways treat insulin resistance in obesity. However, JNK1 knockout mice gain less weight compared with their wild-type control littermates and had slightly greater body temperatures, implying an increase in energy expenditure.⁵¹ Decreasing JNK1 expression using an ASO against JNK1 increases energy expenditure decreased body weight gain and NAFLD, decreased PKC ϵ activation, and improved insulin sensitivity. Thus, although activation of inflammatory pathways are clearly associated with adiposity and insulin resistance, the mechanisms whereby these pathways lead to insulin resistance still require further study.

Ectopic lipid accumulation is also associated with the development of endoplasmic reticulum (ER) stress, or more specifically, activation of the unfolded protein response (UPR). The UPR consists of a highly conserved set of coordinated events that allows a cell to adapt to stimuli that may lead to an increase in misfolded proteins trafficking through the ER. In many instances, the UPR is adaptive. For example, cells that secrete proteins may need to rapidly expand the ER in response to a specific stimulus. For example, the UPR may be critical to allow β -cells to increase insulin secretion. In other tissues, however, activation of the UPR can impair proper cellular function. In this context, the UPR has been implicated in the pathogenesis of insulin resistance.

Activation of the UPR in livers of leptin-deficient *ob/ob* mice⁵² suggests that these pathways may be involved in the pathogenesis of insulin resistance in obese states in rodents as well as in humans.⁵³ Chemical inducers of the UPR impaired insulin signaling,⁵² whereas chemical chaperones that reduce ER stress improved insulin signaling.⁵⁴ Also, markers of the UPR are decreased after surgical induced weight loss,⁵³ but the UPR can also regulate lipogenesis, lipid droplet formation, and lipid storage.^{55,56} Thus, it remains possible that activation of the UPR may primarily alter cellular lipid balance and, via accumulation of lipid intermediates, alter insulin signaling.

These alternate hypotheses were also assessed in the liver biopsy samples obtained from the same cohort previously described.⁵⁰ In contrast to the strong association between hepatic DAG content, PKC ϵ activation and insulin resistance, there was no relationship between plasma cytokine concentration (TNF- α , IL-1 β , IL-6, and CRP) and hepatic cytokine expression or hepatic JNK1 activation and insulin resistance. There was only a partial activation of the unfolded protein in one arm of UPR (ie, the PKR-like endoplasmic reticulum kinase arm); other UPR markers did not correlate with insulin resistance. Thus, additional studies are required to better discern the roles of innate immunity and the UPR in the pathogenesis of insulin resistance with adiposity.

In summary, the development of insulin resistance in adiposity is associated with ectopic lipid accumulation in insulin responsive tissues. The studies reviewed demonstrate the specific role of DAG, as a key activator of nPKCs, which subsequently impair insulin signaling. In skeletal muscle, DAG-mediated activation of PKC θ impairs insulin-stimulated muscle glucose transport. In the liver, DAG-mediated activation of PKC ϵ diminishes the ability of insulin to promote glycogen synthesis and inhibit gluconeogenesis. Of note, although hepatic DAG content is tightly associated with insulin resistance, the association between BMI and insulin resistance is less strong; there is variability in the degree of insulin resistance even among individuals with similar BMI. One possible explanation for this variability may be differences in adipocyte function and this is an area of ongoing investigation.

Adipose tissue dysfunction as a contributor to the metabolic syndrome

Excessive body fat deposition, particularly after a truncal/abdominal pattern of distribution, is a major predictor of insulin resistance and the clustering of abnormalities defining the metabolic syndrome. The presence of metabolic complications of adiposity is, however, not universal in the obese population and it may be observed in subjects with relatively low BMI or body fat content. It is estimated that about 32% of obese adults in the National Health and Nutrition Examination Survey population do not have metabolic abnormalities,⁵⁷ whereas insulin resistance and its complications affect a significant percentage of people who are not obese.^{58–60} This is particularly evident within racial minority groups of the United States.⁵⁷ A major obstacle to significant advances in the field has been a relatively limited focus on adipose tissue dysfunction as etiologic for insulin resistance and its metabolic complications. Shifting the focus from fat mass/distribution to that of adipose tissue dysfunction could help identify novel markers of risk for metabolic abnormalities of lipid metabolism and consequent chronic diseases, including T2DM and CVD.

Metabolically healthy obese persons may not benefit from interventions to reduce risk for adiposity-related chronic diseases, such as CVD and T2DM. More importantly, metabolically unhealthy non-obese persons are not commonly identified and treated for disease prevention. Although waist circumference adds to the specificity of BMI in identifying patients with metabolic complications of adiposity, populations around the world have been shown to have different susceptibilities to insulin resistance and metabolic syndrome for similar waist circumference. Because of this observation, modified cutoff points for specific populations around the world are available to better identify patients at risk.⁶¹ These definitions remain a significant clinical challenge for practical application within the multi-ethnic/multiracial population of the United States.

Recent advances in the understanding of the role played by adipose tissue function on systemic abnormalities of glucose and lipid metabolism promise to provide a practical solution for the clinician. Along this line, effort is being made to identify metabolic determinants of lipid and glucose abnormalities resulting from adipose tissue dysfunction. By studying the difference in ethnic susceptibility to insulin resistance and metabolic syndrome of Asian Indians, a population at increased risk for both CVD and T2DM, it is apparent that severe insulin resistance can be present in lean, young Asian Indians even in the absence of a visceral fat distribution pattern or increased waist circumference.⁵⁸ Studies have identified abnormalities in fatty acid handling by adipose tissue in young, lean normoglycemic Asian Indians compared with persons of European descent with similar body composition and fat distribution. Subsequent investigation suggested a possible role for the glycoprotein ecto-nucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) in adipose tissue dysfunction and insulin resistance of Asian Indians and other ethnic minority groups of the U.S. population.⁶² Mechanistically, it is established that ENPP1 expression in adipocytes is highly regulated during adipogenesis and that its dysregulation is associated with significant changes in adipocyte maturation and TG storage.⁶³ In the murine cell line 3T3L1 (a cell line used to study adipogenesis), ENPP1 overexpression induces defective glucose uptake (cellular insulin resistance) and decreases lipid accumulation (adipocyte maturation). This effect is determined by an interaction between ENPP1 and the alpha subunit of the insulin receptor, which has been shown in other cell lines to decrease activation of the insulin receptor beta subunit and downstream insulin signaling (Fig. 7). ENPP1 expression also impacts adipose tissue metabolism “in vivo.” The AdiposeENPP1-Tg mouse is characterized by increased ENPP1 expression in adipose tissue only.⁶⁴ This experimental condition reproduces findings typically described in the metabolic syndrome. When exposed to a high-fat diet, the AdiposeENPP1-Tg mice have increased plasma free fatty acid levels, low adiponectin, insulin resistance, and increased liver fat deposition, all independent of any increase in fat mass.

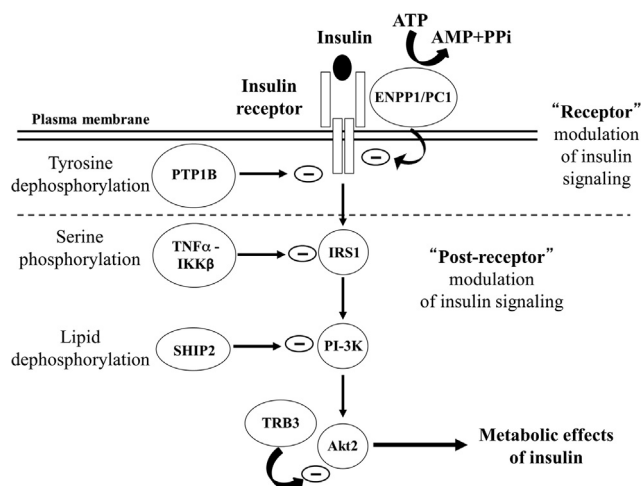


Figure 7 Schematic representation of inhibitors of insulin signaling pathway induced by ENPP1. After binding to the α subunit of its receptor, insulin stimulates a cascade of signaling events. These include tyrosine phosphorylation of both insulin receptor β subunit (autophosphorylation) and IRS-1, and subsequent PI-3K activity and serine-threonine kinase 2 (Akt2; also known as protein kinase B) activation. The inhibitory effects of ENPP1 are mediated via protein-protein interaction with the alpha subunit of the insulin receptor. Reproduced with permission.³⁸⁰ IKK β , I κ B kinase β ; PC1, plasma cell glycoprotein 1; PTP1 B, protein tyrosine phosphatase 1B; SHIP2, Src-homology2-domain-containing inositol 5-phosphatase 2; TRB3, mammalian tribbles homolog 3.

An interpretation of these findings in the AdiposeENPP1-Tg mouse is schematically presented in Figure 8. When caloric balance is in excess to expenditure, maturing adipocytes increase the synthesis of TG and decrease lipolysis. Normally functioning adipose tissue will guarantee an increase in body fat content to “buffer” caloric excess without metabolic abnormalities. Figure 8

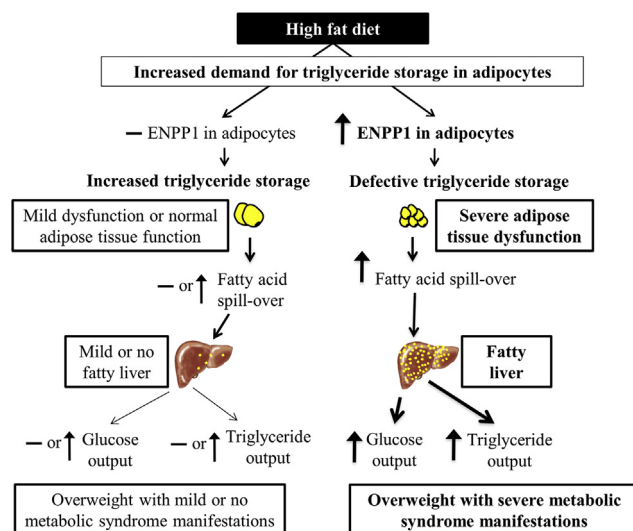


Figure 8 Schematic representation of the effects of ENPP1 on TG storage in adipose tissue and its interaction with diet and weight gain as a determinant of fatty liver and other manifestations of the metabolic syndrome in the AdiposeENPP1-TG mouse. Reproduced with permission.⁶⁴

shows the likely events occurring in the AdiposeENPP1-Tg mouse when a lack of ENPP1 down-regulation determines adipocyte maturation arrest and defective TG storage in adipose tissue. Subsequently, fat redistribution and ectopic deposition in lean tissues, such as the liver ensues. The onset of the metabolic syndrome is then evident even at minimal positive caloric balance and even in the absence of significant weight gain. This would explain the observation of metabolically unhealthy lean persons. The translational value of these findings in the adiposeENPP1-Tg mouse was recently addressed in a study conducted in normoglycemic human volunteers. Increasing ENPP1 expression in adipose tissue is associated with increasing fasting plasma free fatty acid levels, decreasing plasma adiponectin, fatty liver, and declining systemic insulin sensitivity in men. These findings provide support to the hypothesis of a mechanistic association between adipose tissue content of ENPP1 and adipose tissue dysfunction which, in turn, has significant systemic metabolic consequences heralding the onset of the metabolic syndrome.⁶⁵

Additional mechanisms of defective adipocyte maturation leading to adipose tissue dysfunction and systemic metabolic complications are being actively studied and are increasingly the topic of research of many laboratories around the world. It is likely that these ongoing efforts will provide us with better ways to identify and treat patients with the metabolic syndrome who are at heightened risk for related chronic disease complications. At this time, there is a need to evaluate both obese and non-obese people for presence of the metabolic syndrome. Clearly, adiposity is not always accompanied by the metabolic syndrome and therefore does not always associate with increased risk. On the other end, absence of adiposity does not preclude the presence of the metabolic syndrome and high risk for T2DM and CVD.

Adiposity and TGs

Lipoproteins in adiposity with hypertriglyceridemia

TG levels are an aggregate measure of TG content of all circulating lipoproteins with the majority residing in the apolipoprotein (apo) B-containing lipoproteins. These particles function as the primary carriers of TG in blood, transporting TG to the periphery. Apo B-containing lipoproteins are further subdivided into two classes: (1) apo B₄₈-containing chylomicrons and their remnant particles originating from dietary lipid, assembled in the enterocytes of the gut; and (2) apo B₁₀₀-containing particles including VLDL, intermediate-density lipoprotein (IDL), and LDL and a glycoprotein derivatized LDL-like particle, lipoprotein(a). The principal lipoprotein particle secreted by the liver is VLDL with IDL and LDL resulting from progressive delipidation of VLDL particles by postsecretory action of various lipases (eg, LPL, hepatic lipases) as the particles

circulate through peripheral tissues. Adiposity results in resistance to the action of insulin in the liver and peripheral tissues, causing a multitude of alterations in intracellular signaling and changes in substrate handling, ultimately resulting in increased rates of secretion of TG-enriched VLDL particles.⁶⁶ This is often combined with a relative decrease or insufficient LPL activity,⁶⁷ and thus the promotion of incompletely metabolized chylomicron, VLDL, and IDL remnant particles (normally low in concentration in the lean insulin sensitive state) whose accumulation are known to have atherogenic and prothrombotic effects.^{68–70} The high TG content of the secreted VLDL results in high concentrations of small, dense TG-enriched LDL particles⁶⁹ which are more susceptible to oxidation,⁷¹ more readily taken up into the subintimal vascular space, and often characterized as highly atherogenic. This shift toward small dense particles begins at serum TG levels >100 mg/dL, well below the range accepted as abnormal in the current guidelines.⁷² Reduced activity of LPL in the setting of adiposity and insulin resistance frequently leads to varying degrees of incomplete metabolism and clearance of postprandial chylomicrons and high residual concentrations of chylomicron remnant particles. Chylomicrons themselves do not appear to be atherogenic since their very large diameter prevents diffusion into the subendothelial space unless there is significant endothelial damage. Very high TG levels characteristic of chylomicronemia lead to increased plasma viscosity and abnormal blood rheology,^{73,74} leading to flow disturbances and ischemia at the microvascular level. This mechanism has been postulated to be etiologic of TG-related pancreatitis, the most common clinical complication of severe hypertriglyceridemia and chylomicronemia.^{75,76}

Associations with CVD risk

Disordered TG metabolism resulting in nonchylomicron hypertriglyceridemia is one of the five defining features of the metabolic syndrome.⁷⁷ In population-based studies, increased TG levels are associated with increased CVD risk in univariate analysis. This association is ameliorated, but not necessarily eliminated, in multivariable adjusted models when numerous covariates of TG and insulin resistance such as age, gender, BMI, waist size, waist-hip ratio, smoking, exercise, glycemic status, diabetes, and exposure to medications, are taken into account.⁷⁸ From a practical standpoint, this loss of significant association after model adjustment does not suggest that TG is an unimportant biomarker in clinical practice since individual patients cannot be “adjusted” for covariates. It remains important for the clinician to correctly identify the underlying dyslipidemia phenotype, potential targets for treatments, and selection of drug therapy. This is particularly important in T2DM patients where treatment of hypertriglyceridemia may impact microvascular⁷⁹ and possibly major CVD outcomes if hypertriglyceridemia coexists with reduced levels of HDL-C.⁸⁰

Non-HDL-C and apo B appear to be superior measures of atherogenic lipoprotein burden and lipoprotein associated

vascular risk compared with LDL-C levels alone.⁸¹ The National Cholesterol Education Program, Adult Treatment Panel III (NCEP-ATP III) recommends the use of non-HDL-C at TG levels >200 mg/dL as a secondary treatment target, but does not make specific recommendations with regard to measurement of apolipoproteins or use in directing therapy.

Lipoprotein disorders, hypertriglyceridemia, and adiposity

The metabolism of TGs can be affected by numerous dietary, behavioral, and clinical factors leading to hypertriglyceridemia, as summarized in Table 5.⁸² Most important is the effect of high-carbohydrate diets, reduced physical activity, and exercise in the setting of excess visceral fat stores. Regrettably, this triad is common and increasingly prevalent in the western industrialized world with TG levels consistently increasing during the past 3 decades after a similar prevalence of obesity, now with approximately one-third of adults in the United States having fasting TG levels greater than the desirable levels of <150 mg/dL.⁸² To complicate the situation, many common medical conditions often coexist with obesity, and the drugs used to treat them may themselves lead to hypertriglyceridemia (Table 6). Hypertriglyceridemia in this setting frequently behaves as a “two-hit” phenomenon (Fig. 9). In patients with underlying genetic predisposition, such as the relatively common familial combined hyperlipidemia or familial hypertriglyceridemia, or genetic inheritance of the more rare LPL deficiency, apo C-II deficiency, or familial dysbetalipoproteinemia (the first hit), hypertriglyceridemia is often most commonly and/or most fully expressed in the setting of positive caloric balance, physical inactivity, excess visceral fat, insulin resistance, uncontrolled T2DM, untreated hypothyroidism, nephrotic syndrome, acute alcohol consumption (especially in patients with fatty liver), and other secondary causes, such as exposure to therapeutic agents (eg, some antiretroviral agents, some

phenothiazines and secondary antipsychotics, nonselective beta blockers, thiazide diuretics, oral estrogens, glucocorticoids, tamoxifen, and isotretinoin) that promote hypertriglyceridemia (the second hit).⁸³

Diagnosis and classification of hypertriglyceridemic dyslipidemias

Identifying and characterizing hypertriglyceridemic dyslipidemias is an important first step toward defining an optimal treatment strategy.⁸⁴ A very simple and effective diagnostic strategy has been proposed by De Graaf et al,⁸⁵ requiring only apo B and TG levels and TG/apo B ratio for classification (Fig. 10). This classification scheme takes advantage of the ability of apo B to provide a proportional measure of concentration of apo B-containing particles. Thus, a TG/apo B ratio would reflect the amount of TG carried per atherogenic particle, with a greater value suggesting presence of increased TG-rich lipoproteins. As would be expected, abdominal adiposity, metabolic syndrome, and T2DM are ubiquitous secondary etiologies in the classification when chylomicrons, VLDL, or remnant lipoproteins are the lipoprotein species in excess.

Hypertriglyceridemia frequently is a marker of high atherogenic particle burden and apo B levels in excess of that reflected by more traditional measures such as LDL-C when accompanied by increased concentrations of remnant VLDL, IDL, or LDL particles. At one time, the atherogenic risk of excess concentrations of normal-size and composition VLDL particles characteristic of type IV dyslipidemia was generally believed to carry normal or only modestly increased atherogenic risk, the major concern being pancreatitis at sufficiently elevated TG levels.⁸⁶ Later studies of families showed evidence of premature CVD and metabolic syndrome in the setting of familial combined hyperlipidemia (VLDL and LDL excess) as well as familial hypertriglyceridemia (VLDL excess only).⁸⁷

Table 5 Common causes of hypertriglyceridemia

High-carbohydrate diet
Excessive alcohol consumption, especially when combined with high saturated fat diet
Hypothyroidism
Renal disease
Poorly controlled insulinopenic T2DM
Physical inactivity, sedentary lifestyle
Pregnancy
Polycystic ovary syndrome
Excess visceral fat, abdominal adiposity
Hepatic steatosis or steatohepatitis
Autoimmune diseases (eg, SLE with anti-LPL antibodies)
Genetic defects involving apo AV, apo CII, LPL, GPIHBP1, and others
Familial combined hyperlipidemia (FCHL): apo B excess (VLDL and LDL excess), polygenic
Familial hypertriglyceridemia (FHTG): VLDL excess, polygenic
Type III dyslipidemia or dysbetalipoproteinemia:– excess VLDL and IDL remnants, apo E ϵ_2/ϵ_2 genotype

Apo, apolipoprotein; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein; IDL, intermediate-density lipoprotein; LPL, lipoprotein lipase; T2DM, type 2 diabetes mellitus; SLE, systemic lupus erythematosus; VLDL, very-low-density lipoprotein.

Table 6 Drugs associated with hypertriglyceridemia

Thiazides	Beta blockers without alpha antagonist activity
Tamoxifen	Atypical antipsychotics
Glucocorticoids	Sirolimus
Raloxifene	Retinoic acid drugs
Protease inhibitors	Oral estrogens (not transcutaneous)
λ -Asparaginase	α -Interferon
Bile acid sequestrants	

The management of hypertriglyceridemia is directed to the specific lipoprotein in excess and, when possible, the underlying mechanism responsible for its excess. Lifestyle modifications are central to managing hypertriglyceridemia. Aerobic exercise results in increased activity of LPL, increased insulin sensitivity, and increased rates of clearance of TG-rich lipoproteins. Diets that feature a low glycemic index, limit refined carbohydrate, and include a large proportion of fats as omega-3 polyunsaturates tend to lower TG. Diet management differs in the setting of chylomicron excess in which the goal is chronic restriction in total dietary fat intake. During acute illness with markedly elevated TG and chylomicronemia, fasting reduces the rate of chylomicron synthesis. Gastrointestinal/pancreatic lipase inhibition using tetrahydrolipstatin (orlistat) is a useful adjuvant to dietary fat restriction, resulting in further reduction of fat absorption and chylomicron synthesis. Fish oils and omega-3 polyunsaturated fatty acid pharmaceuticals reduce VLDL synthesis and increase TG catabolism. Other dietary fats should be administered as medium chain (C₆-C₁₂) fatty acids in the setting of hyperchylomicronemia because these fats do not participate in the formation of chylomicrons, unlike longer chain fatty acids. Fibric acid derivatives (eg, fenofibrate or gemfibrozil) and the thiazolidinediones (eg, pioglitazone) increase clearance rates of TG-rich lipoproteins.

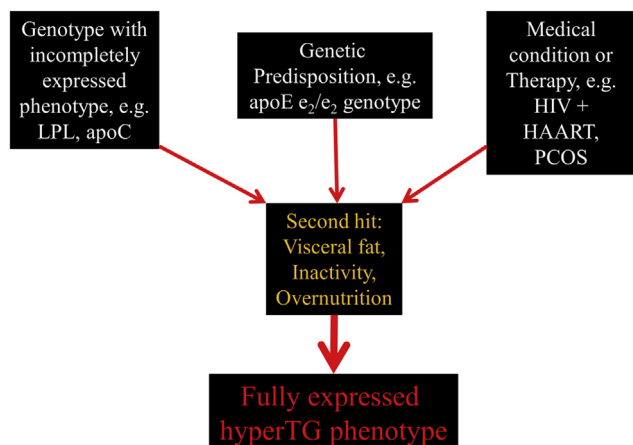


Figure 9 “Two-hit” phenomenon. A genetic predisposition or underlying medical condition defines the susceptibility (the first hit), with the fully expressed hypertriglyceridemic phenotype becoming apparent only in the setting of excess visceral fat, inactivity, insulin resistance, or drug exposure (the second hit).

These drugs find their principal role in the management of dyslipidemia characterized by excesses of VLDL and remnant lipoproteins but are also useful in hyperchylomicronemia. Severe, life-threatening hyperchylomicronemia may require acute management with plasmapheresis.

The statins and nicotinic acid (niacin) have little direct impact on hyperchylomicronemia. These drugs reduce TG levels in the setting of VLDL or VLDL-derived remnant lipoprotein excess, such as in insulin resistance or the primary dyslipidemias characterized by excess of these lipoproteins.

Non-CVD outcomes in chronic adiposity complicated by hypertriglyceridemia

Aside from concern for excess risk of atherosclerosis and macrovascular CVD, adiposity complicated by hypertriglyceridemia is frequently the precursor to T2DM, with its attendant risks of various end-organ complications, particularly microvascular complications involving the retina, kidney, and peripheral sensory neurons/axons. Metabolic syndrome accounted for one-half of the incident T2DM in the Framingham Offspring Cohort over 8 years follow-up with a relative risk of 23.83 (95% confidence interval 5.80–98.01) when at least three of the metabolic syndrome features were present versus none.⁸⁸ The presence of the metabolic syndrome has been shown to predict all-cause mortality in addition to its effects on coronary and total CVD mortality in middle-aged men with a relative risk of 2.43 (95% confidence interval 1.64–3.61).⁸⁹ The ratio of TG to HDL-C (TG/HDL-C), incorporating two of the metabolic syndrome measures, has been shown to predict incident hypertension and diabetes⁹⁰ and is a strong covariate of insulin resistance.⁹¹ The greatest quartile of TG/HDL-C ratio, >3.66, has been shown to predict all-cause mortality in women in the WISE study with suspected myocardial ischemia.⁹²

Until recently, the hazard of adiposity and hypertriglyceridemia to the liver has been underappreciated. The liver hosts much of the metabolic activity involving TG-rich lipoproteins and energy balance and accordingly suffers the consequences of insulin resistance and disordered TG metabolism.⁹³ Fatty infiltration of the liver, also known as hepatic steatosis or NAFLD, is commonly associated with adiposity and hypertriglyceridemia and can result in steatohepatitis, fibrosis, and cirrhosis, resulting in death from end-stage liver disease or hepatocellular carcinoma.⁹⁴ The presence of NAFLD is itself a marker associated with excess CVD risk⁹⁵ as well as adverse effects on arterial structure⁹⁶ and mechanics.⁹⁷

Adiposity and HDLs

HDLs are complex, and their role in the clinical management of patients is a matter of intense worldwide investigation. There is little question that, based on prospective observational cohorts around the world, low serum levels of HDL-C are among the most important predictors of risk for CVD in both

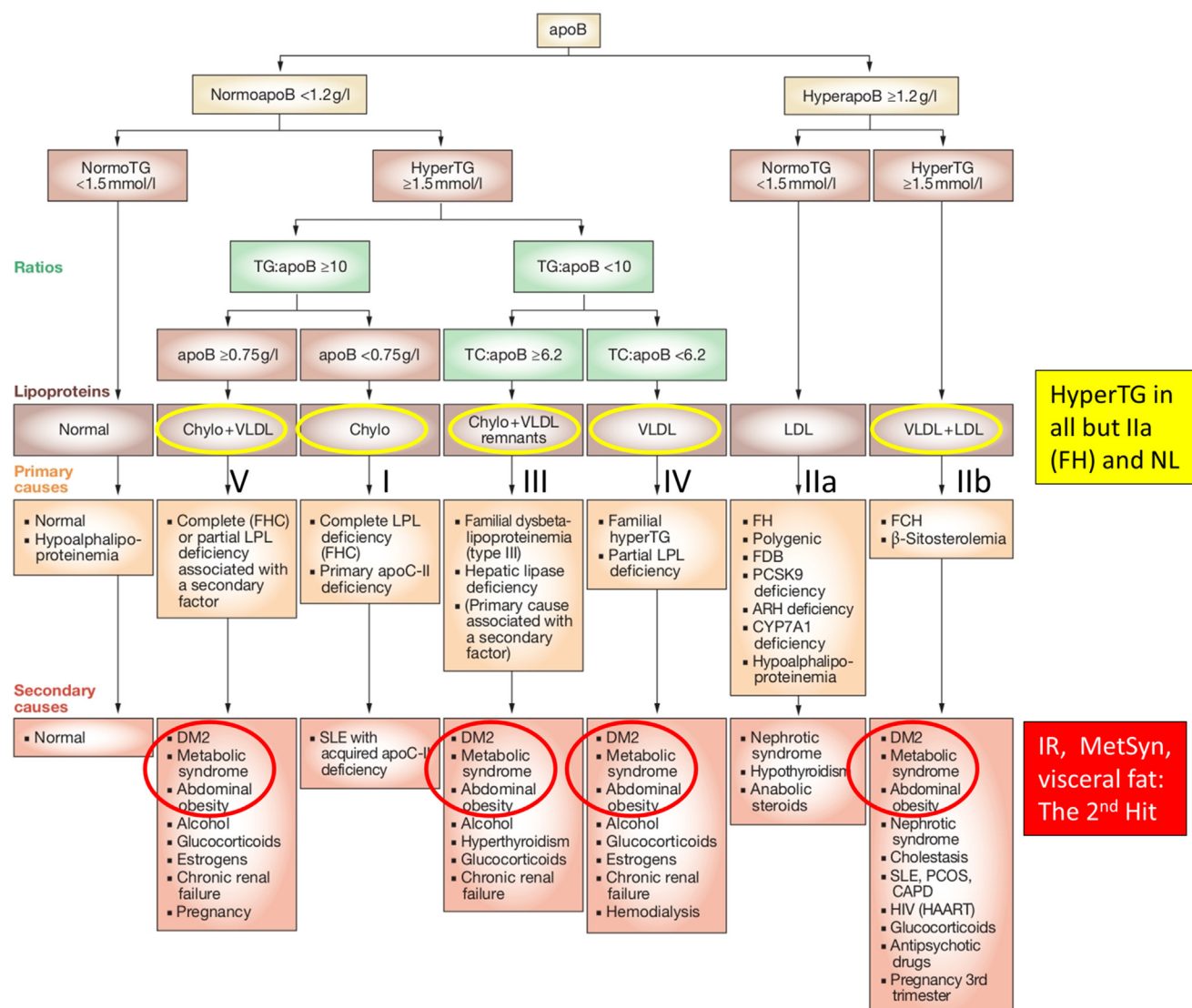


Figure 10 Classification of hypertriglyceridemic dyslipidemias. Adapted from de Graaf et al⁸⁵ and reproduced with permission.

men and women, irrespective of race or ethnicity.^{98,99} The NCEP defines a low HDL-C (<40 mg/dL) as a categorical risk factor for coronary heart disease and recommends that in patients with low HDL-C lifestyle modification be instituted in an effort to increase it.¹⁰⁰ The intravenous infusion of HDLs induces significant atherosclerotic plaque regression over the course of weeks, although it is not yet clear whether this correlates with reductions in acute cardiovascular events.^{101,102} A number of meta-analyses support the importance of increasing HDL-C levels to achieve plaque regression^{103,104} and reduce CV events¹⁰⁵ in patients treated with statins. In post hoc analyses of both the Bezafibrate Infarction Prevention Study¹⁰⁶ and the Air Force/Texas Coronary Atherosclerosis Prevention Study,¹⁰⁷ multivariate regression analysis suggests that the increase in HDL-C induced by lipid-altering drug therapy contributes to overall risk reduction. Similarly, in patients with T2DM, the increase in HDL-C stimulated by pioglitazone correlated highly with atherosclerotic disease regression in both the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation

study¹⁰⁸ and the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone trial.¹⁰⁹ More recently, prospective randomized studies performed with both CETP inhibitors^{110,111} and with niacin^{112,113} have called the therapeutic value of increasing HDL-C levels into question. Multiple innovative approaches for increasing HDL-C and HDL particle number remain in development.

The HDLs remain an area of intense research because of their diverse functionality. The HDL proteome comprises more than 70 distinct proteins.¹¹⁴ The apoproteins, enzymes, globulins, microribonucleic acids, sphingolipids, and complement components comprising HDL's proteome confer a remarkable range of biochemical functions to these lipoproteins.^{115,116} Among the most important is the series of reactions collectively termed reverse cholesterol transport, the process by which HDLs are able to promote the mobilization, externalization, and deliver excess systemic cholesterol back to the liver for disposal. The cholesterol efflux capacity from human macrophages (a metric of HDL function) has a strong inverse association with both

intima-media thickness and likelihood of angiographic coronary artery disease (CAD), independent of HDL-C levels.¹¹⁷

Possible mechanisms by which HDLs have the potential to reduce coronary heart disease are the ability of HDL particles to maintain endothelial integrity, facilitate vascular relaxation, inhibit blood cell adhesion to vascular endothelium, reduce platelet aggregability and coagulation, and promote processes that favor fibrinolysis¹¹⁸; antagonize lipid oxidation, thrombosis, and inflammation¹¹⁹; participate in immunity; and function as a reservoir of apoproteins, among other functions. Under some conditions (as in heightened systemic inflammatory tone), some HDL subspecies appear to have compromised functionality and may actually be proatherogenic.¹²⁰ However, in general, and in contradistinction to apo B₁₀₀-containing lipoproteins, HDLs are viewed as having antiatherogenic functions.

HDL biosynthesis

The HDLs are synthesized by a variety of organs and cell types. Jejunal enterocytes express apoprotein AI (apo A-I), the primary apoprotein constituent of HDL. Apo A-I can be incorporated into chylomicrons; alternatively, apo A-I can be secreted and lipidated on the cell surface by the adenosine 5'-triphosphate binding membrane cassette transport protein A1 (ABCA1). As LPL hydrolyzes TGs in the chylomicron particle, surface coat constituents containing apo A-I are released that can be further lipidated to form HDL. The liver is another important source of apo A-I and lipidates lipid free apo A-I and nascent discoidal HDL via the activity of ABCA1. On the surface of macrophages, HDL is lipidated by the activities of ABCA1, ABCG1, and scavenger receptor BI (SR-BI). Similarly, on the surface of insulin-sensitive adipocytes, HDL biogenesis is promulgated by ABCA1 and SR-BI. A large number of distinct HDL species can be separated based on charge, size, and molecular characteristics.

Adiposity, insulin resistance, and HDL

On the basis of a 26-year follow-up of the original Framingham Cohort, obesity was identified as an independent risk factor for the development of CAD, CV mortality, and congestive heart failure in men, even after investigators controlled for age, cigarette smoking, total cholesterol, systolic blood pressure, left ventricular hypertrophy, and glucose tolerance.¹²¹ Among women, weight correlated with incident risk of CAD, CV mortality, CHF, and stroke after investigators controlled for the aforementioned covariates. Adiposity increases risk for insulin resistance as well as its sequelae, metabolic syndrome, and T2DM. Insulin resistance is devastating to the cardiovascular system because it induces low HDL-C, elevated TG and small, dense LDL particles, hypertension, endothelial dysfunction, glucose intolerance, heightened systemic inflammatory and oxidative tone, and a prothrombotic state.¹²²

A low serum HDL-C (<40 mg/dL in men and <50 mg/dL in women) is a defining feature of the metabolic syndrome. Although there are a large number of genetic polymorphisms that can predispose individuals to a low HDL-C,¹²³ more recent analyses from the Framingham Offspring Study suggests a low HDL-C only augments risk for coronary heart disease if it occurs in the presence of insulin resistance (hazard ratio 2.83 compared with individuals with no insulin resistance and above median HDL-C). There was no significant difference in the cumulative incidence of CV events between the groups with high HDL-C (mean 62 mg/dL) or low HDL-C (mean 42 mg/dL) without insulin resistance. HDL-C is highly responsive to the effects of insulin resistance. In the San Antonio Heart Study, it was estimated that for every 1 mg/dL reduction in HDL-C monitored prospectively, risk for new onset T2DM increases by 4%.¹²⁴

Adiposity and insulin resistance induce a large number of changes in lipid and lipoprotein metabolism that result in the development of a characteristic atherogenic pattern of dyslipidemia.^{125,126} During positive caloric balance, especially if adipocyte proliferation in peripheral subcutaneous adipose tissue is impaired, then adipocytes may become excessively enlarged and adipose tissue accumulation may become physiologically excessive. These anatomic abnormalities often are associated with pathophysiologic consequences such as intracellular stress, hypoxia, as well as a number of pathologic endocrine and immune responses. Additional adipopathic consequences include impairment of energy storage resulting in an increase in circulating free fatty acids that may lead to visceral, periorgan, and perivascular adiposity. Clinically, this is manifest by central adiposity, insulin resistance, and impaired lipid metabolism, most commonly manifest by hypertriglyceridemia and low HDL-C levels. As the liver takes up this excess of fatty acid, it must adjust its metabolism to the influx of excess oxidizable substrate. The fatty acid can undergo β oxidation within the mitochondrial matrix, shunted toward gluconeogenesis via activation of phosphoenolpyruvate carboxykinase, re-esterified into TG via the activity of DAG acyltransferase-2, secreted in VLDL particles, or can be deposited within the hepatic parenchyma and result in hepatic steatosis.

Hypertriglyceridemia is a defining feature of insulin resistance/metabolic syndrome and is a consequence of two metabolic alterations: (1) increased TG-enriched hepatic VLDL secretion; and (2) decreased VLDL and chylomicron TG hydrolysis in plasma secondary to reduced LPL activity. The activity of LPL decreases as the concentration of apo CII (an activator) decreases and apo CIII (an inhibitor) increases.¹²⁷ The mass and activity of LPL can be further suppressed by angiopoietin-like protein 4, which induces a conformational conversion of the catalytically active dimer of LPL into two catalytically inactive monomers.¹²⁸⁻¹³⁰ Insulin resistance is associated with increased expression of angiopoietin-like protein 4.¹³¹ This results in increased serum levels of chylomicron remnants,

VLDL and its remnants (incompletely digested VLDL particles), as well as TGs. With reduced chylomicron lipolysis, less surface coat mass containing apo A-I is released, impacting apo A-I availability and HDL formation. In addition, as VLDLs accumulate, there is increased activity of CETP, an enzyme that catalyzes a 1:1 stoichiometric exchange of TG out of VLDL for cholesterol ester in HDL particles. As the HDLs become progressively more enriched with TG, they become better substrates for lipolysis by hepatic lipase. As the HDLs are progressively lipolyzed, they become thermodynamically unstable and can dissociate apo A-I. The apo A-I can be bound to the megalin-cubilin-amnionless system and metabolized by the proximal tubular epithelium in the kidney, resulting in further reductions in HDL-C. Insulin resistant adipose tissue also has a more direct impact on HDL metabolism. As the adipose tissue mass enlarges and becomes more insulin resistant, it becomes infiltrated with macrophages, which create a proinflammatory milieu. The cytokines released into adipose tissue induce the down regulation of multiple cholesterol transport proteins, including ABCA1, ABCG1, and SR-BI, which decreases HDL lipidation and speciation.¹³²

Insulin plays a significant role in the regulation of hepatic apo A-I expression.^{133,134} There is an insulin response core element in the promoter site of the apo A-I gene that binds the transcription factor Sp1. Insulin can stimulate apo A-I expression by activating two different signaling cascades: one regulated by *ras-raf* which activates mitogen-activated protein kinase, and the other by PI-3K which activates PKC (Fig. 11).¹³⁵ When the liver becomes insulin resistant, these pathways are adversely affected, resulting in reduced apo A-I transcription and HDL synthesis. There is also a carbohydrate response element in the promoter for apo A-I that facilitates the inhibition of gene expression in the presence of high glucose levels.^{134,136} Insulin resistance is a proinflammatory state. Insulin resistant adipose tissue produces large amounts of TNF- α and IL-1. Both of these cytokines can bind to a cytokine response element that suppresses apo A-I expression.¹³⁷ Hepatic nuclear factor 4 also suppresses expression of apo A-I. Among Japanese men with T2DM, the T130I mutation is associated with lower serum HDL-C compared to noncarriers of this gene.¹³⁸ The regulation of hepatic apo A-I expression is clearly complex and adversely impacted at multiple levels in the insulin resistant state.

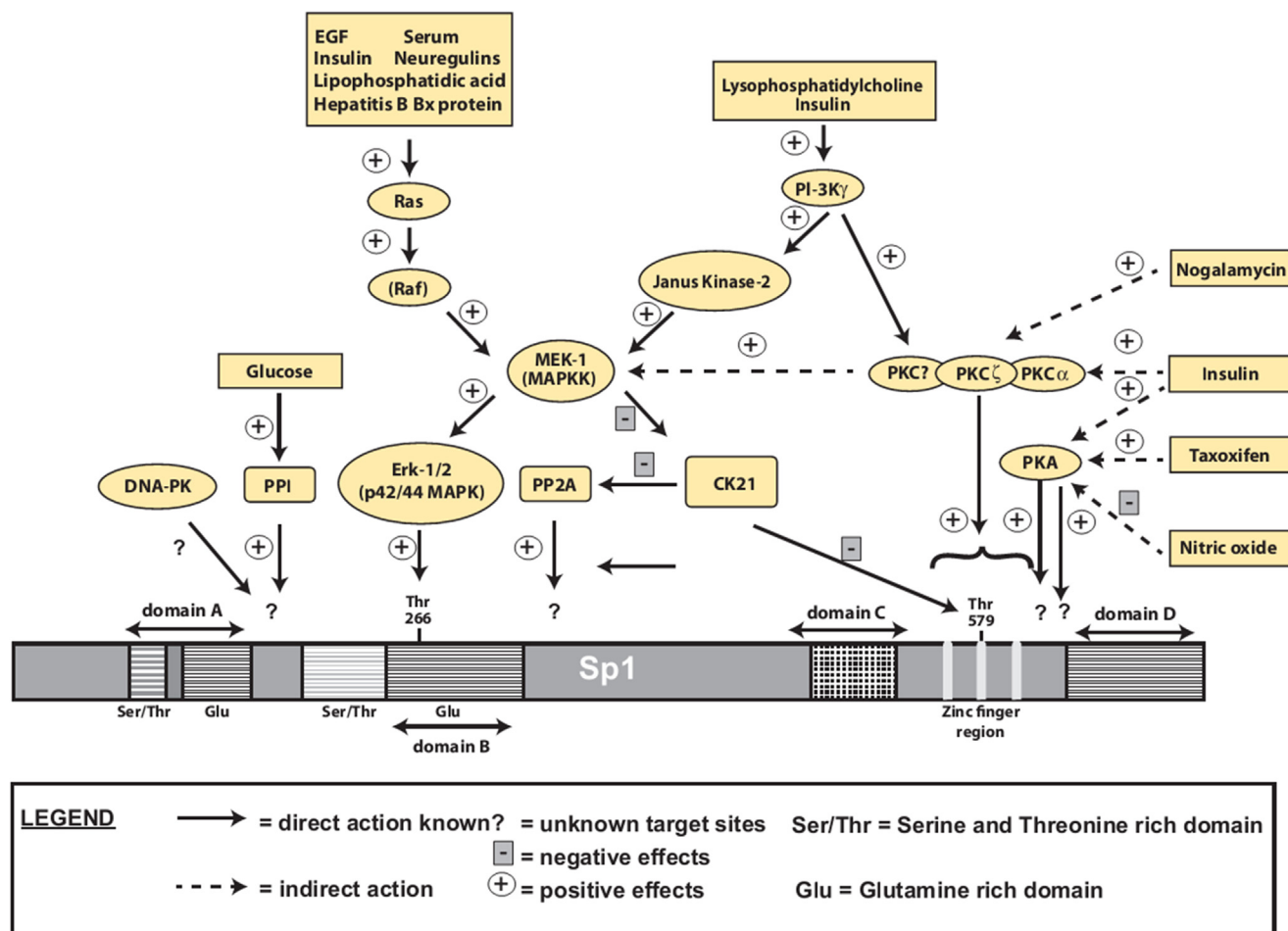


Figure 11 Signaling pathways regulating Sp1 modulation of apoprotein A-I gene expression. Reproduced with permission.¹³⁴

The kidney can also play a role in modulating serum HDL-C levels. In the Prevention of Renal and Vascular End-Stage Disease study, serum HDL-C and apo A-I levels had an inverse linear correlation with creatine clearance and estimated glomerular filtration (GFR) rate (ie, the greater the renal filtration capacity, the lower the serum HDL-C) in patients without established renal disease.¹³⁹ These relationships were independent of central adiposity, insulin resistance, or serum TG level. Adiposity and insulin resistance are both associated with increased GFR and renal plasma flow.^{140,141} Glomerular hyperfiltration with marked elevation of GFR is pathological, can be a manifestation of chronic insulin resistance and T2DM, and appears to potentiate HDL renal elimination.

Adiposity complicated by either insulin resistance or T2DM is also associated with impaired HDL functionality. There is growing evidence that in the setting of insulin resistance, HDL tends to become more oxidized and glycated, changes that correlate with reduced capacity for reverse cholesterol transport and antioxidative function^{142,143} The clusterin content of HDL decreases markedly with rising adiposity and insulin resistance.¹⁴⁴ Clusterin exerts potent antiatherogenic effects and is an important inhibitor of complement activation and tissue injury.

HDL as regulator of islet cell insulin secretion

There is considerable evidence supporting the role of lipotoxicity and intrapancreatic steatosis in the pancreatic dysfunction manifested in insulin resistance and T2DM. Pancreatic β -islet cells express the LDL receptor. The exposure of islet cells to LDL/VLDL,¹⁴⁵ oxidized LDL,¹⁴⁶ or IL-1¹⁴⁷ reduces insulin secretion and can trigger apoptosis, resulting in a progressive loss of islet cell mass. HDL prevents islet cell apoptosis in response to each of these stimuli. In the case of LDL- and VLDL-induced cytotoxicity, HDL reduces islet cell apoptosis by inhibiting the cleavage of caspase-3 and activating protein kinase B.

Apo A-I and HDL also appear to play a key role in regulating islet cell insulin secretion. Mice with islet cell inactivation of ABCA1 have impaired glucose tolerance and insulin secretion.¹⁴⁸ Apo A-I can stimulate insulin mRNA expression and secretion by islet cells by binding to either ABCA1 or SR-BI; HDL particles can also stimulate islet cell insulin secretion by binding to ABCG1.¹⁴⁹ HDL also appears to be able to modulate the capacity of skeletal myocytes to take up and metabolize glucose. In a reaction that is clathrin dependent, apo A-I is endocytosed and stimulates the phosphorylation and activation of AMP-activated protein kinase and acetyl CoA carboxylase.¹⁵⁰ This in turn results in increased glucose uptake and metabolism, reduced gluconeogenesis, and increased fatty acid β -oxidation in the mitochondrial matrix. The intravenous infusion of HDL into humans with T2DM confirms that HDL stimulates insulin secretion, glucose uptake, and the phosphorylation and activation of acetyl CoA carboxylase and AMP-activated protein kinase.¹⁵¹ When cultured skeletal

myocytes extracted from patients with T2DM are exposed to either HDL or apo A-I, glucose uptake is stimulated in a reaction that is dependent on ABCA1 and activation of the calcium/calmodulin-dependent protein kinase and AMP-activated protein kinase pathways.¹⁵¹

These data strongly suggest that apo A-I and HDL participate in glucose homeostasis. This creates a possible vicious circle: as insulin resistance worsens, serum levels of HDL decrease secondary to decreased production and increased catabolism; as HDL concentrations decrease, islet cell insulin secretory capacity and skeletal muscle cell (the major sink for glucose disposal) glucose uptake and catabolism decrease, resulting in progressive impairment in glucose tolerance and, ultimately, T2DM. It remains to be elucidated whether therapeutic modulation of HDL in vivo through lifestyle modification or pharmacologic intervention results in improved glucose homeostasis. However, a post hoc evaluation from the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events trial suggests that HDL elevation with torcetrapib did in fact impact glucose homeostasis.¹⁵²

Adiposity and LDLs

The metabolic risk factor that has been one of the major foci of preventive efforts, namely high circulating concentrations of LDL-C, is not part of the diagnostic rubric of the metabolic syndrome. Is this because LDL-C is not associated with adiposity? There are two components to the answer. The first has to do with operational issues. With current guidelines, the metabolic syndrome establishes the identification of a clustering of coronary heart disease risk factors, which may help prompt clinicians to recognize secondary lipid goals, such as non-HDL-C when TGs are >200 mg/dL.¹⁵³ The second reason for giving less attention to LDL-C when considering the adiposity problem is that the cholesterol component of LDL is only weakly related to body fat mass in cross sectional community based studies. However, emerging data suggest that beyond absolute LDL-C values, the composition of LDL may change as TGs increase and HDL-C decreases. It is this change in LDL composition that may reduce the apparent correlation between weight gain and rising LDL-C. Understanding the true role that LDL may play in the risk of CVD the obesity epidemic may require LDL be measured in ways other than cholesterol content.

Adiposity and LDL in observational studies

Total cholesterol and LDL-C often have little correlation with increasing adiposity in many cross sectional community based studies.¹⁵⁴ In the initial cohort of the Framingham Heart Study, Kannel et al used ultracentrifugal analysis of LDL (Sf 0-12), IDL (Sf 12-20), and two components of VLDL: small VLDL (Sf 20-200) and large VLDL (Sf 200 to 400). Larger Sf values translate into more lipid and particularly more TG in each lipoprotein class. These

analyses found only a weak correlation of LDL and IDL with body weight in those ages 30 to 49 years, and no correlation in those 50 to 64 years. Both VLDL components had strong positive relationships to excess body weight across all age groups.¹⁵⁵ More recently, the Framingham Offspring study reported that BMI is positively but relatively weakly related to LDL-C levels in men ($n = 1566$) and in women ($n = 1627$).¹⁵⁶ The mean age of this population was 49 in both gender groups, and the relationship of LDL-C was most evident in those younger than 50 years of age. The strongest relationship of LDL-C to BMI occurred in persons of low and desirable body weight (ie, BMI $20 < 25 \text{ kg/m}^2$). However, there was no relationship in those with BMI $\geq 25 \text{ kg/m}^2$ and even a reduction in the very obese.¹⁵⁶ As the population surpasses defined cut-off points for being overweight, the positive correlation with excess body fat is no longer evident and LDL-C tends to fall in the highly obese (Fig. 12). The major exception is the subgroups of obese patients whose major adipose tissue accumulation is within the abdominal cavity and referred to as the viscerally obese.¹⁵⁷ However, in the Epic-Norfolk study, consisting of 20,021 British men and women, investigators used several anthropomorphic measures to assess adiposity and to relate these to CVD risk factors.¹⁵⁸ The study authors chose the waist-hip ratio as the preferred method and noted a consistent increase in TGs and decrease in HDL-C within each quintile of this measure from lowest to highest. In men, no differences were observed in LDL-C levels over the full range of quintile values (Fig. 13A). In women, there was a consistent increase in LDL-C but the absolute change was very small, increasing from 142 to 167 mg/dL (3.69 to 4.37 mmol/L; Fig. 13B). This population was recruited between 1993 and 1997 and included an age range from 45 to 79 years. It should be noted that Epic-Norfolk does not reflect the range of obesity currently seen in the United States. The median BMI in the lowest quintile was 23.9 kg/m² for men and women and in the fifth quintile, the value was only 28.8 kg/m² for women and 29.1 kg/m² for men. So, there were very few obese people by the standard of BMI $\geq 30 \text{ kg/m}^2$.

Krauss et al¹⁵⁹ noted a reduced LDL particle size (measured by gradient gel electrophoresis) and reduced cholesterol content to be characteristic of subjects with greater TGs and lower HDL-C and therefore, by inference, with

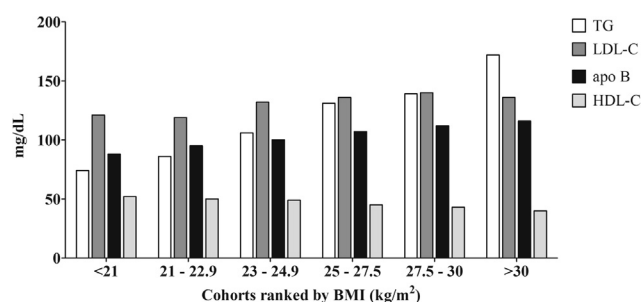


Figure 12 BMI and lipid risk factors for men in the Framingham Offspring Study.¹⁵⁶

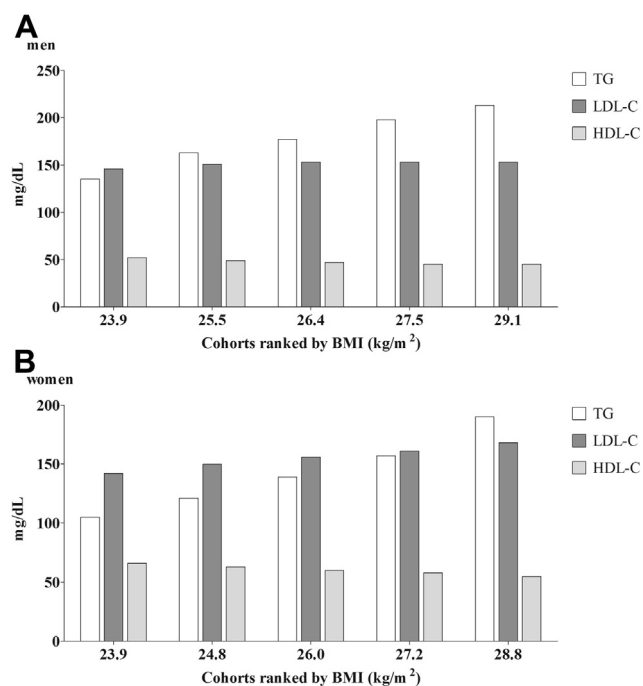


Figure 13 Lipids and lipoproteins in 9036 men (A) and 10,098 women (B) in the Epic-Norfolk study.¹⁵⁸

adiposity. The reduced content of cholesterol and cholesterol ester in LDL (and HDL) has been adequately explained by the action of CETP acting to exchange TG from the increased VLDL and chylomicron remnants often associated with adiposity. In population studies, small LDL particles were characteristic of subgroups with a greater incidence of coronary events and this linkage of elevated TGs, small dense LDL, and low HDL-C was initially referred to as the “atherogenic lipoprotein phenotype,”⁷² albeit conceded that isolated LDL-C levels can also be atherogenic. Within the context of the adipocentric paradigm, an alternative description of this specific lipid pattern often associated with pathogenic adipose tissue (as noted above) would be adiposopathic dyslipidemia.

Diagnosing the metabolic syndrome by current guidelines is another approach to this entity in clinical medicine. During the same period, it was recognized by Sniderman that the prevalence of relatively elevated apo B was more common than elevated LDL-C in patients with CAD.¹⁶⁰ Because there is only one molecule of apo B in each atherogenic lipoprotein, which includes LDL, VLDL, and Lp(a) particles, this finding was consistent with the finding of small dense LDL in population studies. The dissociation of LDL-C and apo B measures has been observed in patients who subsequently developed CAD compared with normal controls in many subsequent studies.¹⁶¹

These studies have provided strong evidence that when properly measured, apo B is a better predictor of major vascular events in observational studies than LDL-C, particularly when TG levels are increased. This finding implies that the number of atherogenic particles, including the number of LDL particles, is a stronger risk factor than

LDL-C. In the Insulin Resistance Atherosclerosis Study, apo B measures were significantly correlated with both waist circumference and BMI, whereas LDL-C was not.¹⁶² When apo B was statistically adjusted for its relationship to LDL-C, there was an even stronger correlation with the anthropometric measures. Apo B but not LDL-C has been found to have a positive relationship to a series of inflammatory markers in these high risk obese patients.

The development of nuclear magnetic resonance (NMR) spectroscopy has provided another independent method for estimating number of lipoprotein particles of different size in a given patient. Particle numbers have been measured in several community based studies and in cohorts from clinical trials. This measure has been found to be particularly powerful in determining differences in particle number and cholesterol content of LDL in T2DM populations. As assessed by NMR, the relationship of LDL particle number to measures of adiposity is also informative. In the Multiethnic Study of Atherosclerosis, (Fig. 14) patients who had relatively high LDL particle number compared with LDL-C were significantly more obese.¹⁶³ These patients also had a significantly greater incidence of vascular events associated with particle number over a wide spectrum of LDL-C values. This confirmed the findings in a 14.8-year follow-up of the Framingham Offspring Study (n = 3066) in which particle number was a much better predictor of CVD events. In Japanese men, with or without diabetes, BMI correlated with apo B and small LDL particles but not with LDL-C. LDL particle number and apo B appear to relate to adiposity but this relationship is not altered by diabetes.¹⁶⁴ This appears to be different in T2DM women who have been reported to have significantly greater apo B concentrations after adjustment for adiposity.¹⁶²

Adiposity and the kinetics of apo B-containing lipoproteins

Does increased body fat alter the production rates of VLDL and LDL or change their clearance rates from the bloodstream? The individual variability of the production rates for apo B and TGs and the difficulty in making these

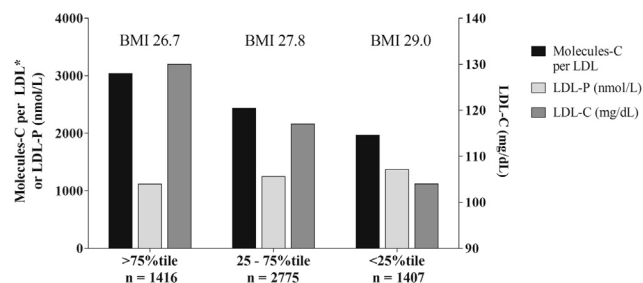


Figure 14 BMI and LDL composition in the multiethnic study of atherosclerosis (ie, MESA) study.¹⁶³ Values were adjusted for age, gender, and race. *Molecules-C per LDL = estimate of the number of cholesterol molecules per LDL particle (LDL-P) was calculated by dividing LDL-C (mmol/L) by LDL-P (nmol/L).

measurements has limited our ability to study sufficient numbers of patients to obtain a definitive answer to this question at the population level. Greater production rates of apo B in the LDL density range (1450 mg/day vs 934 mg/day) were found in six obese men compared to six men of more normal weight.¹⁶⁵ The LDL-C was slightly lower in the obese (111 mg/dL vs 145 mg/dL) and the cholesterol to apo B ratio was lower, suggesting small dense LDL in the obese. These same authors noted that apo B synthesis and clearance rates were also greater in patients with coronary heart disease when they were matched for age, weight, and plasma lipid levels. Regarding weight loss intervention in obese patients, data regarding changes in production of TGs as well as VLDL and LDL apo B suggest high synthesis rates may contribute to vascular disease in adiposity without altering the plasma LDL-C. Unfortunately, total plasma apo B and particle number were not assessed in these early studies. Early kinetic studies also demonstrated TG synthesis rates increase by feeding high carbohydrate diets without changing the rate of apo B synthesis in the VLDL and LDL fractions.¹⁶⁶ The composition of VLDL leaving the liver can change with metabolic interventions such as diet.

It is widely accepted that visceral adiposity and the accompanying increased waist circumference are important markers of the development of greater TGs, lower HDL-C, insulin resistance, and other related risk factors. The mechanism by which this particular distribution of adipose tissue changes lipoprotein metabolism is not yet fully defined. The synthesis rates of VLDL apo B are increased in this disorder.¹⁶⁷ This subgroup of obese patients is also more likely to have increased levels of LDL-C as well as increased total apo B. In a study of 48 viscerally obese patients in which the authors used stable isotopes to label and measure the kinetics of apo B, the authors found greater synthesis rates of both apo B and apo CIII.¹⁶⁷ The apo CIII concentration was strongly related to the reduced percent conversion of VLDL apo B into LDL apo B. The greater apo B in LDL was also correlated with a reduction in clearance rates of LDL apo B. These data are compatible with other data showing that apo CIII reduces both lipase action and reduces clearance of VLDL remnants as well as LDL from the plasma.¹⁶⁸⁻¹⁷⁰ High fatty acid flow from the visceral fat (and other fat depots), as well as changes in cytokines related to this fat deposit, are believed to enhance the synthesis of VLDL TGs, apo B, and apo CIII.¹⁶⁷ Reduction of this fat storage is well demonstrated to reduce these lipoprotein abnormalities. Recent studies have found a subset of small dense LDL particles to contain a tightly bound component of apo CIII.¹⁷¹ This may be particularly important because of the growing evidence that apo CIII in LDL is a marker of enhanced CAD risk.¹⁷² However, it is not yet known whether this apo CIII-enriched LDL is related to adiposity per se.

Adiposity as measured by BMI, waist circumference, or other anthropomorphic measures is associated with all characteristics of the metabolic syndrome. However, as noted

before, the relationship to increased LDL-C is not found in most observational studies. The exception is in the subgroup with visceral adiposity. However, the greater TGs and lower HDL-C in adiposity is a consistent finding. In these patients, apo B is often increased and the LDL particles are increased in number but reduced in cholesterol content. Thus, LDL does play a role in increased CVD risk in obese patients. In the viscerally obese, enhanced apo B and apo CIII synthesis may be particularly atherogenic due to the prolonged residence times of VLDL remnants and LDL particles containing apo CIII as well as some more specific effect of apo CIII in the LDL fraction. Weight loss is effective in reducing TGs, increasing HDL-C, and converting small, dense LDL particles into larger, fewer, and more buoyant ones. In some patients, the reduction into the desirable range of BMI $<25 \text{ kg/m}^2$ may be required to achieve lipoproteins of desirable number and composition. These compositional changes in lipoproteins may provide more accurate means of assessment of risk reduction than changes in LDL-C with various forms of therapy in the future.

Bariatric endocrinology and the management of adiposopathy

The relationship between the accumulation of intra-abdominal or visceral fat and dyslipidemia was formalized by the NCEP-ATP III.^{77,173} In their report defining the metabolic syndrome, abdominal adiposity measured by waist circumference (>40 inches in men and >35 inches in women) was part of a clustering of CVD risk factors, along with high blood pressure ($\geq 130/85$ mmHg), high fasting plasma glucose concentration (≥ 100 mg/dL), hypertriglyceridemia (≥ 150 mg/dL), and low plasma levels of HDL-C (<40 mg/dL in men and <50 mg/dL in women). By definition, any patient who has three or more of the five diagnostic criteria listed by NCEP-ATP III has metabolic syndrome. *The International Classification of Diseases*, 9th edition, introduced a code for metabolic syndrome, 277.7, validating it as a clinical condition that warrants intervention.

The traditional approach to the dyslipidemia of overweight and obesity has been the treatment of lipids and lipoproteins. In addition to the dietary restriction of fat and normalization of glycemia in patients with T2DM, medications that lower TGs and raise the HDL-C include statins, fibrates, niacin, some omega-3 fatty acid preparations, thiazolidinediones and more recently GLP-1 agonists.^{174–179} The recommendation to help patients lose weight, although universally endorsed, is infrequently followed by the formal implementation of a weight management program with pharmacological intervention.

Bariatric endocrinology

Bariatric endocrinology is the medical subspecialty that deals with the diagnosis and treatment of adiposopathy. In this paradigm, it is not sufficient to treat the complications

of adipose tissue dysfunction (ie, dyslipidemia, hyperglycemia, hypertension, hypogonadism, hyperuricemia). Rather, a major goal of treatment is to return adipose tissue to normal physiology. The stratification of health risk is performed not on the basis of body mass alone. The regional distribution of fat, and the effect that this distribution has on adipose tissue function, allow for better treatment choices. Given that many patients with hypertension, dyslipidemia and hyperglycemia are at a BMI that is defined as lean for Caucasian populations, and that up to one third of patients with stage III obesity do not have these metabolic derangements, BMI alone is not adequate for risk stratification.¹⁸⁰

In clinical practice the simple measurement of waist circumference is the single most cost-effective way of beginning the risk stratification process.¹⁸⁰ Dual-energy x-ray absorptiometry (DXA) measurement of body composition has become a “gold standard” for the evaluation of regional fat distribution.^{181–185} DXA body composition analysis allows for the measurement of temporal and regional characteristics of lean and fat mass, including truncal fat and visceral adipose tissue (VAT). It is now possible to identify individuals who have low percentages of truncal fat or VAT despite high BMIs. Conversely, it is possible to find individuals with high percentage truncal fat or VAT, but whose BMI places them in the lean body weight category. DXA VAT measurements are very highly correlated to computed tomography measurements and can be done in a much safer and cost-effective way in an outpatient office setting.

Visceral fat thresholds for metabolic risk have been established based on currently available data. At 100 cm^2 there is increased risk, and at 160 cm^2 there is high risk of adiposopathy (Fig. 15).

With more precise measurements of lean and fat mass made possible by DXA body composition analysis, a classification of overweight and obesity based on the fat mass index is now possible (Table 7). The fat mass index is more precise than BMI to define risk that is gender specific and better correlated with adiposopathy.

The International Society for Clinical Densitometrists has formalized the use of DXA body composition analysis as the new standard of care. However, DXA body composition analysis does not yet have a current procedural terminology code for billing third-party payers. Because of this, the number of centers that have implemented this technology is limited. However, both waist circumference measurements and DXA body composition analysis, as it becomes more widely implemented, provide better risk stratification than BMI alone.

A second level of risk stratification comes from lab testing. In addition to the well-established clinical laboratory tests used in mainstream clinical practice, new assays may also help better characterize the presence of adiposopathy (Table 8). The adipocyte hormones leptin and adiponectin represent emerging tools for risk stratification in patients with adiposopathy. Leptin levels increase with increasing

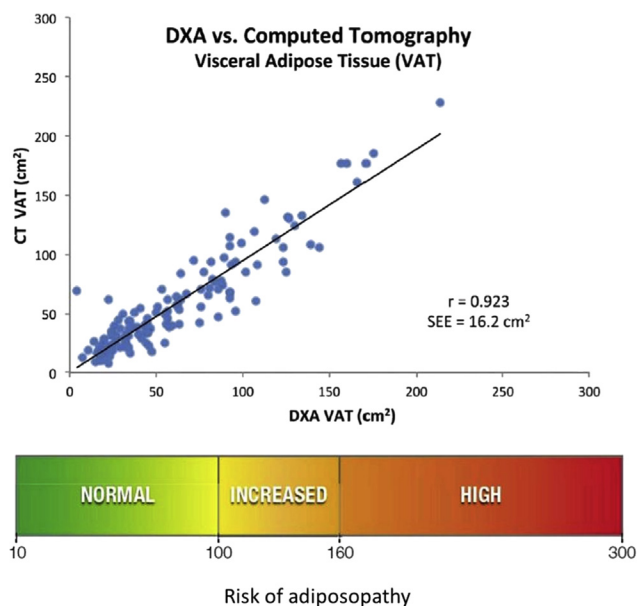


Figure 15 DXA visceral adipose tissue (VAT) measurements. There is a strong correlation between VAT measurements obtained with computed tomography (CT), and those obtained with DXA. On the basis of currently available data, there are established thresholds of DXA-derived VAT for risk of adiposopathy, and consequently cardiovascular disease. Adapted from Kelly³⁸¹ and reproduced with permission.

fat mass. Conversely, adiponectin levels will decrease in patients with adiposopathy. An increase in the leptin to adiponectin ratio over time places patients at a greater risk of metabolic and cardiovascular complications. A decreasing ratio of leptin to adiponectin, on the other hand, signals a return of adipose tissue function toward normal.¹⁸⁶ For example, a high leptin to adiponectin ratio is a predictor of intima media thickness of the common carotid artery, and this is more common in people with obesity (BMI ≥ 30 kg/m²) than in non-obese subjects (ratio of 1.20 vs 0.42, respectively, $P < .001$).¹⁸⁷ Although not standardized or approved by the FDA, assays are now available in reference labs for clinical use of these adipose tissue-derived hormones.

Principles of bariatric endocrinology

Bariatric medicine involves the diagnosis and management of the causes, prevention, and treatment of overweight

Table 7 Classification of fat mass based on DXA-derived FMI

Classification	Male FMI, kg/m ²	Female FMI, kg/m ²
Severe fat deficit	<2	<3.5
Moderate fat deficit	2 to <2.3	3.5 to <4
Mild fat deficit	2.3 to <3	4 to <5
Normal	3 to 6	5 to 9
Excess fat	>6 to 9	>9 to 13
Obese class I	>9 to 12	>13 to 17
Obese class II	>12 to 15	>17 to 21
Obese class III	>15	>21

DXA, dual-energy x-ray absorptiometry; FMI, fat mass index.

Table 8 Selected biomarkers of adiposopathy

- Hyperinsulinemia/hyperglycemia
- High TG/low HDL-C
- Elevated free fatty acids
- Elevated leptin
- Decreased adiponectin
- Increasing leptin to adiponectin ratio over time
- Increased TNF- α
- Activation of renin-angiotensin-aldosterone
- Hypoandrogenemia in men
- Hyperandrogenemia in women

HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TNF- α , tumor necrosis factor- α .

and obesity. Within the context of the abnormal hormonal and metabolic disease consequences of excessive body fat, the following principles of bariatric endocrinology are advanced to mainstream the diagnosis and treatment of adiposopathy:

- Adiposopathy is more common with increasing fat mass, but adiposopathy may occur at any BMI.
 - As discussed previously, although dyslipidemia has an increased prevalence with increasing BMI (Fig. 1), not all patients who are overweight or obese have metabolic disease. Conversely, as noted in Figure 16, not all patients with metabolic disease are overweight or obese. Nonetheless, whether it be dyslipidemia, or T2DM or hypertension, approximately three-quarters or more of patients with these metabolic diseases are either overweight or obese. This makes the important point that although adiposopathy is a common promoter of metabolic disease, dyslipidemia, T2DM, and hypertension have other potential causes that are largely independent of adipocyte and adipose tissue function (Table 9).
- Risk stratification of excessive body fat should not be performed on the basis of BMI alone but rather based on adipose tissue function, defined with anthropometric measures and laboratory data targeted to anticipated potential adverse metabolic consequences (eg, lipid levels, glucose levels, blood pressure measurements, sex hormones, etc.). BMI alone is limited because it is a measurement of not only fat mass, but also muscle mass and bone mass, which may substantially vary between individuals.
- All patients with adiposopathy should have as a goal of treatment to return adipose tissue function to normal.
- Overweight and obesity should be treated as other chronic diseases, an example of which is T2DM (Table 10; Fig. 17).
- The team approach to adiposity and adiposopathy, with multicomponent behavioral interventions, improves the likelihood of individual patient success.¹⁸⁸
- Behavior modification to treat adiposopathy should be extended to the support structure of the individual patient (ie, home and work environments).

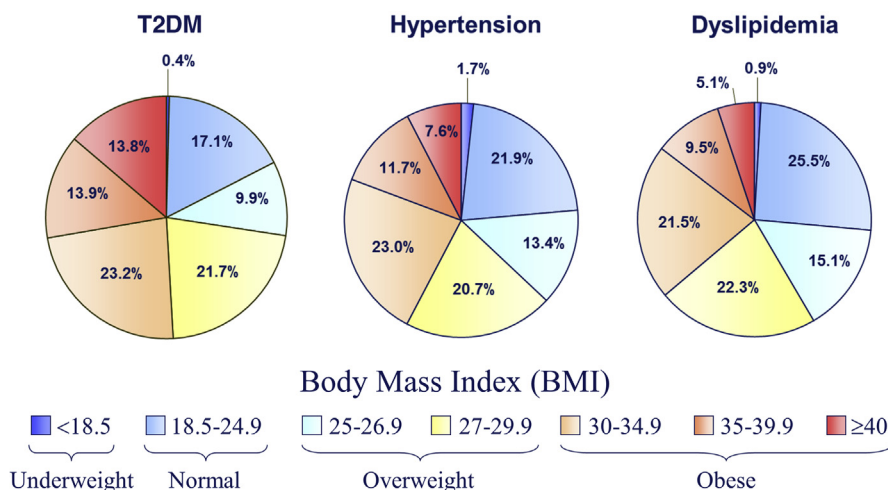


Figure 16 BMI distribution among patients with metabolic diseases. In general, metabolic disease definitions are based on measurements whose abnormalities significantly increase the risk of adverse clinical outcomes. The fact that these metabolic diseases often have a unified underlying pathophysiologic process may help to explain why the distributions of BMI for type 2 diabetes mellitus, hypertension, and dyslipidemia are generally similar. Adapted and reproduced with permission.³⁸²

- Therapies to achieve reductions in intra-abdominal dysfunctional fat, and fat mass in general, should not have term limits.¹⁸⁹⁻¹⁹¹
 - Single agent therapy is expected to have limited efficacy over time.¹⁹²⁻¹⁹⁴
 - The goal of therapy is to lose 5–10% of entry body weight over 6–12 months.
 - Failure of monotherapy to reach treatment goals warrants consideration of combination therapy.^{195,196}

- Bariatric surgery should be reserved for individuals who are truly refractory to weight loss in a structured environment with a team of health care professionals dedicated to treatment of overweight and obesity.^{197,198}
- Although national and state agency efforts to prevent adiposity are welcome and extremely important for the health of the nation, we must allow overweight or obese patients, especially those with adiposopathy, access to the care they need.^{199,200}
 - Obsolete laws and regulations should be replaced to allow care of the overweight and/or obese patient, including the use of all approved weight management interventions.
 - Third-party payers should have policies regarding adiposity and adiposopathy that are consistent with other chronic diseases.
 - Legislative bodies and the media should be educated on the cost to society of not treating overweight and obesity.²⁰¹
- The historical bias against overweight and obesity as a disease can be overcome when society focuses on treatments for adiposity and adiposopathy.

Table 9 Examples of diseases other than adiposopathy that cause common metabolic diseases

Dyslipidemia
Untreated hypothyroidism
Poorly controlled T2DM
Certain types of liver or kidney diseases
Genetic dyslipidemias
T2DM
Hemochromatosis
Chronic pancreatitis
Hypercortisolism
Excessive growth hormone
Genetic syndromes of insulin resistance
Genetic syndromes of decreased pancreatic function
High blood pressure
Pheochromocytoma
Primary hyperaldosteronism
Hypercortisolism
Hyperthyroidism
Renal artery stenosis
Various kidney diseases
Familial or genetic syndromes

Although metabolic diseases are often promoted by the pathogenic hormonal and immune dysfunction of adipocytes and adipose tissue, dyslipidemia, type 2 diabetes mellitus (T2DM), and high blood pressure have other potential causes independent of adipocyte and adipose tissue function. Reproduced with permission.⁶

Nutrition, weight loss, and lipid and lipoprotein effects

Lifestyle modification including reduced energy intake, increased physical activity, and behavior modification represents the “gold standard” for achieving and maintaining weight loss. The Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults (The Evidence Report) recommend a deficit of 500 to 1000 kcal/day as an integral part of a weight loss program.²⁰²

Table 10 Model of chronic disease management

T2DM	Overweight and adiposity
Initial workup/risk assessment	Initial workup/risk assessment
Institute treatment	Institute treatment
Patient and family education	Patient and family education
Glucose self-monitoring	Step count and weekly weight
Quarterly office assessments: Follow-up HbA1c, BMI, BP	Quarterly office assessments: follow-up BMI, BP, WC
Periodic screening for complications and risk re-stratification	Periodic screening for complications and risk re-stratification

BMI, body mass index; BP, blood pressure; HbA1C, hemoglobin A1c; T2DM, type 2 diabetes mellitus; WC, waist circumference.

Based on a 2009 Gallup Poll, almost one-half of Americans who reported being above their ideal body weight also reported that they seriously attempted to lose weight.²⁰³ Overweight and obese participants in the 2003 Behavioral Risk Factor Surveillance System (143,386 individuals ages ≥18 years) reported implementing different strategies for weight loss, including a low-fat (high-carbohydrate)/low-calorie diet with or without physical activity, as well as increased physical activity independent of diet.²⁰⁴ By far, the preferred strategy was adopting a low-fat, high-carbohydrate, low-calorie diet plus physical activity (64% of the respondents). There are numerous calorie-reduced, weight-loss diets that vary widely in their nutrient profile, especially macronutrient composition. Many have been evaluated for effects on long-term weight loss and risk factors for CVD, most notably lipids and lipoproteins.

Change in BMI and body weight in response to different weight-loss interventions

In a systematic review and meta-analysis of weight loss clinical trials including a variety of interventions (n = 80 studies with 26,455 subjects) by Franz et al,²⁰⁵ mean weight loss was 5 to 8.5 kg (5 to 9%) during the first 6 months. In studies with a duration of 48 months, weight loss was 3 to 6 kg (3 to 6%), indicating some weight regain. In the studies that were conducted for 48 months that did not use drug therapy, diet plus exercise and diet alone resulted in comparable weight loss of 3 to 4 kg. Interestingly, most weight loss occurred during the first 6 months of the weight loss programs. Similar findings were reported by Dansinger et al²⁰⁶ in a meta-analysis of 46 weight loss trials that reported the effect of dietary counseling versus usual care interventions on weight loss for up to 60 months. Again, by 6 to 12 months, subjects lost 5 kg (6% of BW or 2 BMI units). After 3 years, typically half of the weight lost had been regained. In this meta-analysis, the authors reported a change of approximately - 0.1 BMI units per month from 3 to 12 months of the weight loss intervention and a regain of about 0.02 to 0.03 BMI units per month during the weight maintenance phases. On the basis of the studies by Franz et al²⁰⁵ and Dansinger et al,²⁰⁶ the extent of weight loss is modest during the first year and some weight gain is expected thereafter, if not before. Nonetheless, collectively, the results of these two studies demonstrate that there is an approximate 3 kg loss of body weight in studies of at least 48 months of duration irrespective of diet type.

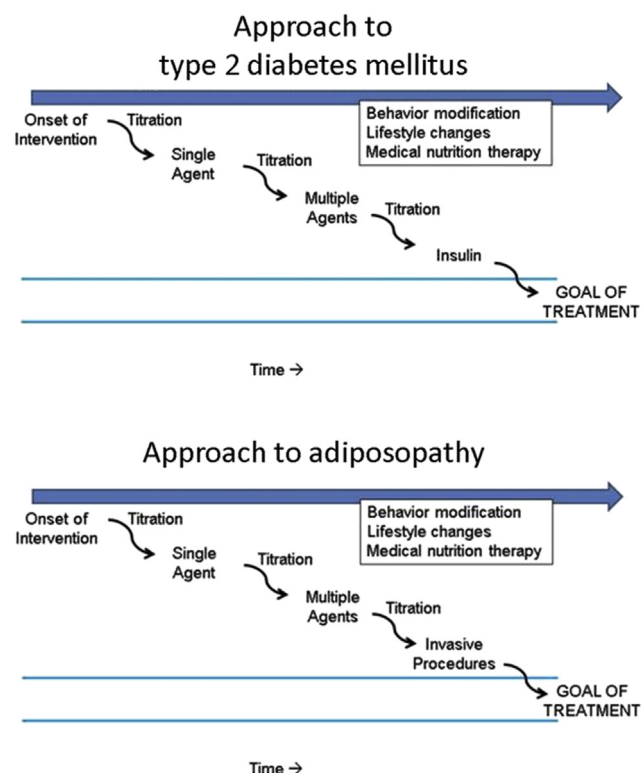


Figure 17 Accepted models of chronic disease management as a practical future approach to treatment of adiposity and adiposopathy.

Effects of weight loss on lipids and lipoproteins

The NCEP-ATPIII recommends weight reduction as part of LDL-C-lowering therapy for overweight/obese persons. The NCEP notes that losing ~4.5 kg of body weight is projected to reduce LDL-C by 5 to 8%. In a meta-analysis of 70 weight loss studies that evaluated the effects of weight loss on lipids and lipoproteins, for every 1-kg decrease in body weight, there was a 1.93 mg/dL decrease in total cholesterol; a 0.77 mg/dL decrease in LDL-C; a 0.27 mg/dL decrease in HDL-C during active weight loss; a 0.35 mg/dL increase in HDL-C with stabilized weight; and a 1.33 mg/dL decrease in TGs.²⁰⁷ In this report, studies

conducted between 1951 and 1989 were summarized with over 2000 subjects. The average weight loss was 16.6 ± 12.6 kg (SD), which is very high compared with the weight loss (3 kg) reported by Franz et al²⁰⁵ and Dansinger et al.²⁰⁶ The study by Dattilo and Kris-Etherton²⁰⁷ reported the following changes in lipids and lipoproteins in response to a 16.6 kg weight loss: -30 mg/dL for total cholesterol; -15 mg/dL for LDL-C; -3.5 mg/dL for HDL-C during active weight loss and 5.4 mg/dL during stable weight; and -58.5 mg/dL for TG. Based on data from these studies^{205–207} LDL-C would be expected to decrease 2.3 mg/dL and TG by 3.99 mg/dL per kg body weight loss. Collectively, a modest weight loss occurs in response to a weight loss intervention with a consequent modest effect on lipids and lipoproteins. Thus, potential benefits of dietary interventions, such as decreasing saturated fat (SFA), trans fat, and dietary cholesterol, and increasing viscous fiber and plant sterols/stanols result in improved lipid levels, as well as possible lipid benefits from the fat weight loss that may accompany such nutritional intervention.

During the past decade, many studies have evaluated different weight loss diets in an attempt to identify the one that promotes the greatest weight loss and weight loss maintenance. Many of these studies also assessed the effects of these diets on lipids and lipoproteins. The studies that have been conducted evaluated greater protein/lower carbohydrate versus greater carbohydrate/low-fat diets, as well as higher fat (specifically Mediterranean-style diets) on both weight loss and the lipid/lipoprotein profile. Moreover, this research has been conducted in various population groups including individuals with, and at risk for, T2DM. There have been two reviews in which investigators evaluated low-fat versus low-carbohydrate weight-loss diets on weight loss and CVD risk factors.^{208,209} In another recent meta-analysis,²¹⁰ researchers evaluated the effects of a high-protein (25 to 35% of energy), low-fat diet ($\leq 30\%$ of energy) versus a lower protein (12%–18% of energy), and low-fat diet ($\leq 30\%$ of energy). Twenty-four trials that included 1063 individuals satisfied the search criteria. In this meta-analysis, the authors reported weight loss and lipid/lipoprotein changes in subjects followed for \geq or <12 weeks on the two weight-loss diets. In the studies that lasted for ≥ 12 weeks, the range of weight loss was 4.2 to 11.4 kg in the high-protein compared with 3.7 to 9.6 kg in the lower-protein group. For the studies that lasted for <12 weeks, the range of weight loss was 3.4 to 9.2 kg in the high-protein group compared with 1 to 7.2 kg in the lower-protein group. A weighted mean analysis demonstrated that the weight loss was similar in both diet categories. The meta-analysis concluded that compared with a lower-protein diet, a high-protein diet produced greater reductions in TG; however, there were no differences between diets for changes in total cholesterol, LDL-C, or HDL-C. The ranges for change in lipids were grouped by study duration (≥ 12 weeks and <12 weeks). For studies ≥ 12 weeks, TG ranged from -9.7 mg/dL to

-65.5 mg/dL (high-protein diet range: -22.1 mg/dL to -65.4 mg/dL; lower protein diet range: -9.7 mg/dL to -53.1 mg/dL); total cholesterol ranged from -5.0 mg/dL to -34.8 mg/dL; LDL-C ranged from $+14.7$ mg/dL to -27.5 mg/dL; HDL-C ranged from $+15.1$ mg/dL to -8.9 mg/dL. For studies <12 weeks, TG ranged from $+8.0$ mg/dL to -109.8 mg/dL (high-protein diet range: -14.2 mg/dL to -109.8 mg/dL; lower protein diet range: $+8.0$ mg/dL to -75.3 mg/dL); total cholesterol ranged from -1.9 mg/dL to -49.1 mg/dL; LDL-C ranged from -1.2 mg/dL to -38.7 mg/dL; HDL-C ranged from $+7.0$ mg/dL to -6.9 mg/dL. In addition, there have been several large randomized controlled clinical trials that have evaluated the effects, both of different dietary patterns and interventions on weight loss and associated CVD risk factors.^{211–215}

Table 11 summarizes the weight loss studies published since 2002 that have evaluated the effects of weight loss (via different diets) on the amount of weight loss, as well as lipid and lipoprotein responses. These studies have been categorized by weight-loss interventions that lasted up to 6 months, which resulted in decreased LDL-C levels ($n = 10$); weight-loss interventions that lasted up to 6 months, which resulted in no change in LDL-C levels ($n = 14$); weight-loss interventions that were greater than 6 months, which resulted in decreased LDL-C levels ($n = 10$); weight-loss interventions that were greater than 6 months, which resulted in no change in LDL-C levels ($n = 12$). The study designs varied appreciably and, consequently, the lipid and lipoprotein results are variable. Nonetheless, there are some salient conclusions that can be drawn about weight loss via dietary intervention:

- *Extent of weight loss.* The amount of weight loss varies considerably, ranging from an average of no weight loss to an average loss >10 kg. Higher-protein/lower-carbohydrate diets often promote greater weight loss compared with higher-carbohydrate/low-fat diets by 6 months, after which time the magnitude of weight loss is similar.
- *Extent of TG reduction.* Perhaps no lipid parameter responds better to nutritional intervention (and increased physical activity) than TG levels. As with other metabolic parameters (such as glucose and hemoglobin A1c), the degree to which TG levels decrease is dependent on the baseline value, with higher baseline TG levels typically having the potential for greatest reduction. In addition, the amount of weight loss affects the TG-lowering response, with greater weight loss resulting in a greater reduction. The type of nutritional intervention also is of significance, in that weight loss achieved in overweight patients by lower carbohydrate diets would be expected to lower TG more than weight loss achieved by higher carbohydrate diets.
- *Extent of LDL-C reduction.* In nearly all weight-loss interventions in which individuals were not taking lipid-lowering medications, LDL-C reductions were

concomitant with weight reduction that typically occurs from 3 to 6 months. Over this timeline in response to higher protein/lower carbohydrate weight loss diets, LDL-C may increase temporarily (in the short term) followed by an eventual decrease as weight loss continues.^{211,212,216} Conversely, higher carbohydrate/lower fat diets cause a more immediate LDL-C lowering response that stabilizes over time.^{212,215} In general, very high carbohydrate/very low fat diets elicit an LDL-C lowering effect but also an HDL-C lowering as well as TG-lowering effect, the latter is not as great as reported for a higher protein/lower carbohydrate diet.^{211,213,217}

- One of the complexities of understanding the effect of weight loss on LDL-C is that weight changes during a weight loss (and weight maintenance) intervention vary. Typically, weight loss occurs and is followed by weight maintenance, which may also result in partial or total weight regain. Compared with the weight-loss period, individuals consume more calories and SFA during the weight maintenance or weight regain period, which would be expected to cause a potential rebound in LDL-C. This could explain why during weight loss LDL-C decreases, and when weight loss slows and/or stops or weight regain occurs, LDL-C drifts upward, and in some instances returns to pre-study levels. In studies that have shown a sustained decrease in LDL-C throughout the study, even though some weight regain has occurred, this could be explained by an effective weight loss and/or a decrease in SFA compared to baseline. In many weight loss trials, study populations include individuals who are severely obese (BMI >35 kg/m²) and have metabolic syndrome or T2DM. As a result, 25% to 75% of the population being studied may be on lipid-lowering medications. Such populations have baseline LDL-C values that are >130 mg/dL (near optimal or above optimal levels). Although LDL-C reductions in these groups are not significant, there is a consistent downward trend that tracks closely with weight loss.^{216,218,219}
- *Changes in other lipids/lipoproteins.* The HDL-C response is variable and is affected both by weight loss and by the type of dietary intervention. Higher-carbohydrate/low-fat diets typically decrease HDL-C or have no effect, whereas higher-protein/lower-carbohydrate diets elicit an increase in HDL-C.²⁰⁹ It is important to appreciate that during weight loss HDL-C may decrease below baseline, whereas after weight loss is maintained, HDL-C may increase above baseline.²⁰⁷

In summary, numerous weight loss studies have been conducted over the past decade using different dietary interventions. As is evident from the summarized results presented in Table 11, the lipid and lipoprotein responses are highly variable. Nonetheless, based on the summary studies presented in Table 11 of approximately 2 to 7 kg weight loss (note there are some studies that reported lesser or greater weight loss), a weight loss of 4.5 kg

would be expected to decrease total cholesterol by about 9 mg/dL, LDL-C 4 mg/dL, HDL-C (during weight loss) 1.2 mg/dL and increase HDL-C 1.6 mg/dL (during weight maintenance), and decrease TG 6 mg/dL (based on the regression coefficients reported by Dattilo and Kris-Etherton²⁰⁷). These calculations are in agreement with the recent meta-analysis by Wycherley et al,²¹⁰ who reported an average weight loss of 7 to 8 kg in weight-loss studies of ≥12 weeks. Importantly, the lipid/lipoprotein changes are modest and highly variable. This is particularly evident in the meta-analysis by Wycherley et al,²¹⁰ which demonstrates marked variation in lipid/lipoprotein responses to weight loss. Some studies in Table 11 reported an increase in LDL-C, even back to baseline levels, whereas others reported a sustained decrease or a modest decrease compared to baseline. Weight loss modestly increases HDL-C in longer-term studies although there are some exceptions. Of note, however, is that HDL-C is affected by the weight-loss diet used; a higher-carbohydrate/low-fat diet decreases HDL-C, whereas a higher-protein/lower-carbohydrate diet and a higher-fat diet do not. Also, weight loss is associated with a decrease in TG. Despite all the research and permutations in experimental designs, the reality is that the average changes in all lipids/lipoproteins in response to weight loss are modest although exceptions can be observed in selected individual studies.

Physical activity, weight loss, and dyslipidemia

The association of physically active lifestyles and adiposity has been demonstrated in epidemiologic studies.²²⁰ The relationship between physical activity and dyslipidemia is less clear but reasonably correlated with changes in adiposity, fat mass, and body weight. This issue is far more complex particularly when recognizing the considerable inter-individual variation in both weight loss and lipoprotein response to a given dose of energy expenditure and all of the associated variables (Table 12). The following summarizes data on the relationship between physical activity and adiposity (including weight loss) and how various doses of physical activity can impact lipids and lipoproteins. Physical activity here refers to any physical activity that increases energy expenditure and, unless otherwise stated, aerobic endurance exercise.

Exercise and weight loss

The evidence remains consistent that increasing calorie expenditure by increasing physical activity is necessary for improved weight-loss outcomes and weight maintenance.^{221–223} There is also a clear weight loss benefit when exercise is systematically added to dietary modification.²²⁴ From a clinical (practical) standpoint, weight loss achieved with exercise training alone often does not

generate the degree of weight loss often observed with caloric intake restriction.²²⁰ However, exercise of sufficient quantity can significantly reduce body weight when the energy deficit is held constant and other factors affecting energy balance are controlled.^{225,226} There are advantages of exercise intervention, especially when implemented in combination with nutritional interventions. In randomized controlled trials, approximately 1 hour of daily moderate aerobic exercise produces at least as much fat loss as equivalent caloric restriction, with resultant greater insulin action.²²⁶ Weight loss induced by exercise without energy restriction prevents the decreases in resting metabolic rate typically associated with weight loss by energy restriction alone. This suggests that exercise may be the preferable mode of weight loss for the prevention of weight regain. It also has been demonstrated that there is a significant enhancement of weight loss when at least 150 min per week of physical activity is added to restriction of energy intake.²²⁷

There is a preferential reduction in intramuscular fat and visceral adipose tissue with exercise-induced weight loss compared with caloric restriction particularly after 1 year of exercise training.^{228,229} Aerobic exercise-induced loss of thigh intramuscular adipose tissue in men is associated with increases in LDL and HDL particle sizes, both of which represent improvements in dyslipidemia.²³⁰

There appear to be gender differences in exercise-generated weight loss while on ad libitum diets. Men are more likely to lose weight whereas women tend to prevent weight gain.²³¹ In the Heritage Family Study, men and women 16–65 years of age, two races (African Americans and white), and variable body composition were given 20 weeks of cycle ergometry endurance training, 3 days per week.²³² When analyzed by group, women, African Americans, and children did not lose weight with such training. Men lost a greater amount of fat than women, but there were no other differences on the basis of sex, race, or age. Women lost less subcutaneous (skinfold) fat than men, less abdominal visceral fat, and less total fat. This gender difference is consistent with an earlier meta-analysis of exercise generated weight loss studies.²³³

Exercise and adiposity reduction

Exercise without weight loss has also been shown to be helpful in men and women for reducing total and abdominal fat and preventing further increases in adiposity.²³⁴ As little as 20 min of moderate-intensity daily physical activity with an energy expenditure of <1500 kcal/week is generally associated with modest reductions (5%–10%) in abdominal visceral fat.²³⁵ In a large prospective cohort study (EPIC, European Prospective Investigation into Cancer and Nutrition) where 84,511 men and 203,987 women were followed for 5.1 years investigators concluded that a higher level of

physical activity reduces abdominal adiposity independent of baseline and changes in body weight.²³⁶

Inactivity and adiposity

A direct link between physical inactivity and the accumulation of visceral fat has also been demonstrated.²³⁷ One intervention was associated with a 7% increase in intra-abdominal fat mass, measured by magnetic resonance scanning, without a change in total fat mass while total fat-free mass and BMI decreased. It has been suggested that physical inactivity is an independent cause of fat accumulation, which is a source of systemic inflammation for which exercise appears to have an anti-inflammatory effect.²³⁸

Exercise, lipids, and lipoproteins

There is a wide variation in the LDL-C response to exercise training; however, some studies have shown exercise-generated reductions in LDL-C of 4–7% as well as increases in HDL-C of 4% to 25% depending on baseline lipid values at training volumes of 1200–2200 kcal/week.^{239,240} Most exercise trials support between 700 and nearly 2000 kcal of exercise per week to significantly alter HDL-C and, to a lesser extent, LDL-C levels.²⁴¹ Very few controlled exercise trials have been conducted on patients with dyslipidemia with most evaluating those with normal or modestly elevated TGs and/or LDL-C.

In general, fat weight reduction is required for the most favorable blood lipid response in those who have elevated total and LDL-C. This volume of exercise (150 min or more per week, optimally 250–300 min per week or ≥ 2000 kcal per week) is similar to that recommended for long-term weight control.²²³ If exercise is of sufficient volume, exercise intensity is not of primary importance in improving the lipid profile, although most research supports a minimum intensity of at least 40% of peak work capacity.²²³ Any effect on lipids and lipoproteins of the intensity of exercise is small as compared with that of the volume of exercise, ie, kcal expended per week.²⁴¹ This may be one reason why many of the resistance training studies have shown little if any reduction in LDL-C and or TGs, as such training may induce inadequate energy expenditure. Some resistance training studies have reported slight-to-moderate reductions in total and LDL-C and others reporting no change.^{242,243} It is likely that the blood lipid response to strength training is related to total net energy expenditure of the session, as it is with aerobic endurance exercise. One example of a relatively high energy expenditure resistance-training session is low-resistance, high-repetition circuit weight training performed for extended periods and approaching 300 kcal or more per session similar to 30 to 35 minutes of moderate intensity aerobic exercise.^{244,245}

Table 11 Changes in Weight and CVD Risk Following Short and Long Term Weight Loss Interventions

Reference	Study Duration	Subjects	Study design; Intervention Groups	Body Weight/ Body Fat	Other Parameters
Weight Loss Studies UP TO 6 MONTHS Which Resulted in DECREASED LDL-C Levels					
Krauss et al., 2006 ³³⁸	13 weeks	N=178 overweight men Mean BMI=29.2	Parallel arm: 1 wk basal diet (54% carbohydrate; CHO); random assignment to basal diet or 1 of 3 low CHO diets (26% CHO + low SFA, 26% CHO + high SFA, and 39% CHO) for 3 weeks; weight loss was then induced (-1000 kcal/day) for 5 weeks followed by weight stabilization for 4 weeks	Body weight decreased similarly across all groups (~5 kg) with the majority of weight loss occurring during the weight loss phase.	All groups experienced reductions in LDL-C during the diet change phase (stable weight) – the greatest reductions were seen in the 26% CHO/low SFA diet and the 54% CHO diet. The 54% CHO and 39% CHO diet groups experienced further reductions in LDL-C during weight loss while the 26% CHO groups had a slight increase. HDL-C did not change significantly during either phase.
Volek et al. 2004 ³³⁹	4 weeks per treatment period	N=13 moderately overweight women Mean BMI=29.6	Cross-over; low-carbohydrate diet (LCD; <10% CHO) vs. low-fat diet (LFD; <30% fat) energy deficit of 500 kcal/d for both groups	SD between groups: 2.96 kg (LCD) vs. -1.06 (LFD); p<0.05	Fasting TC, LDL-C, and HDL-C were significantly lower after the low fat diet compared to LCD (p<0.05). TC -2 mg/dL vs. -13 mg/dL; LDL-C -6 mg/dL vs. +6 mg/dL; HDL-C +1 mg/dL vs. -4/mg/dL. Values represent low fat vs. low CHO diets respectively. Both groups reduced TG from baseline but there was no difference between groups (-10 mg/dL vs. -20 mg/dL, for the low fat and LCD groups respectively).
Aude et al., 2004 ³⁴⁰	12 weeks	N=60 males and females; normal and overweight Mean BMI=35	Parallel arm; NCEP (55% CHO, 15% PRO, 30% fat), or a modified LCD consisting of three phases for 12 weeks: <i>Phase One (two weeks):</i> 10% CHO, 28% PRO, 62% fat <i>Phase Two (two weeks):</i> 27% CHO, 30% PRO, 43% fat <i>Phase Three (eight weeks):</i> 28% CHO, 33% PRO, 39% fat). Diets were 1,300 kcal for women and 1,600 kcal for men	SD between groups: -13.6 lb (LCD) vs. -7.5 lb (NCEP) p=0.02	TC levels were similarly reduced by both diets, and LDL-C levels were not significantly different between the 2 groups. However, LDL-C levels were significantly reduced in the NCEP group (-6.4 mg/dL; p=0.05) but not the LCD group (-3.9 mg/dL; p=0.48). There were no significant differences between groups regarding HDL values. The NCEP group experienced a significant reduction in HDL-C levels (-3.8 mg/dL; p=0.006) but the LCD group did not (-1.3 mg/dL; p=0.46). TG levels were not significantly different between the groups. They were significantly lowered within the LCD group (-42.0 mg/dL; p=0.003) but not the NCEP group (-15.2 mg/dL; p=0.20). The ratio of total cholesterol concentration to HDL-C concentration was not significantly changed by either diet.

Sharman et al., 2004 ^{341,342}	12 weeks; two consecutive six-week periods.	N=15 overweight males Mean BMI=34.3	Cross-over; VLCD (<10% kcals from carbohydrate) or LFD (<30% kcals from fat). Both diets were energy deficient	Both the LCD and LFD resulted in significant within group decreases in body mass (-6.5kg, p<0.01 and -3.7kg, p<0.01, respectively), the differences between groups was not reported	Serum TC was significantly reduced by both the very low-carbohydrate (-11%) and low-fat (-15%) diets, with no difference in the extent of the decrease. LDL-C was significantly reduced only by the low-fat diet (-18%). HDL-C was not affected by either diet but there was a trend for the TC/HDL-C ratio to decrease after consumption of both diets (p=0.10). TG and the TG/HDL-C ratio were significantly reduced only by the very low-carbohydrate diet (-44 and -42%, respectively). oxLDL was not affected by either diet.
Bradley et al., 2009 ³⁴³	8 weeks	N=24 overweight and obese males and females Mean BMI=34	Parallel arm; LCD (20% CHO) vs. LFD (60% CHO); energy deficit of 500 kcal/d for both groups	NSD between groups: 7.6% (LCD) vs. -7.1% (LFD); within group difference p<0.01	The only significant difference in lipid profiles between the two diets was change in TG (p=0.01). This difference reflected a significant reduction in TG after the LCD (-60 mg/dL). Within the low fat diet group TC (-34 mg/dL), LDL-C (-17 mg/dL) and HDL-C (-10 mg/dL) were all significantly reduced (p<0.01). Within the LCD group there were no significant changes in TC or HDL-C; the reduction in LDL-C just reached significance (-14 mg/dL; p=0.05).
Tay et al., 2008 ³⁴⁴	24 weeks	N=88 abdominally obese males and females Mean BMI=34	Parallel arm; Energy-restricted (30% deficit), VLCD vs. HCD diet. VLCD=4% CHO, 35% PRO, 61% fat (20% SFA); HCD =46% CHO, 24% PRO, 30% fat (<8% SFA)	NSD between groups: -11.9 kg (VLCD) vs. -10.1 kg (HCD); p=0.17	The VLCD diet produced greater decreases in TG (VLCD -0.64 +/- 0.62 mmol/L, HCD -0.35 +/- 0.49 mmol/L; p=0.01) and increases in HDL-C (VLCD 0.25 +/- 0.28 mmol/L, HCD 0.08 +/- 0.17 mmol/L; p=0.002). LDL-C decreased in the HCD diet but remained unchanged in the VLCD (VLCD 0.06 +/- 0.58 mmol/L, HCD -0.46 +/- 0.71 mmol/L; p<0.001). However, a high degree of individual variability for the LDL-C response in the VLCD diet was observed, with 24% of individuals reporting an increase of at least 10%.

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Table 11 (continued)

Reference	Study Duration	Subjects	Study design; Intervention Groups	Body Weight/ Body Fat	Other Parameters
Muzio et al., 2007 (Italy) ³⁴⁵	5 months	N=100 obese males and females Mean BMI=37	Parallel arm; LCD (48% CHO, 19% PRO, 33% FAT) vs. HCD (65% CHO, 13% PRO, 22% FAT), energy deficit of 500 kcal	92% of subjects in the HCD group and 84% in LCD group reached a wt loss of >5%	At the end of the study period TC and TG decreased significantly in both groups whereas HDL-C did not change from baseline. The LCD was associated with a greater decrease in SBP and TG than the low fat diet (p<0.05) LDL-C only decreased with the low fat diet (~5%; p<0.01) and there was no between group difference.
Layman et al., 2003 ³⁴⁶	10 weeks; 4 weeks controlled feeding, 6 wks free living with menus provided	N=24 overweight women Mean BMI=30	Parallel arm; High PRO group (30% PRO/41% CHO) vs. Low PRO Group (16% PRO/ 58% CHO)	NSD between groups: -7.5 kg (hi PRO) vs. -6.96 kg (Lo PRO) Body fat loss was greater in the hi PRO group (14.4% vs. 12.2%) while lean body mass loss was greater in the Lo PRO group, however these values did not reach significance	After the first 4 wk of the treatments with food intake monitored in the research facility, TC decreased in the Hi Pro Group by 10.0% (0.58 mmol/L) and LDL-C by 10.5% (0.40 mmol/L). Similarly, TC decreased by 11.2% (0.55 mmol/L) in the Low Pro Group and LDL-C by 14.3% (0.45 mmol/L). These changes were maintained at wk 10. HDL-C values decreased in both groups at wk 2 and 4, but were not different from baseline at wk 10. Fasting TG was reduced significantly in the Hi Pro Group, with the values ranging from 16 to 23% below initial baseline values.
Parker, et al., 2002 ³⁴⁷	12 weeks	N=54 obese males and females with T2DM Mean BMI=34	Parallel arm; High PRO diet (28% PRO, 42% CHO, 28% fat vs. Low PRO diet (16% PRO, 55% CHO, 26% fat); 8 wks energy restriction of 1600 kcal/d followed by 4 wks energy balance	NSD between groups: -5.2 kg for both groups. Hi PRO group lost significantly more total (5.3 vs. 2.8 kg, p=0.009) and abdominal (1.3 vs. 0.7 kg, p=0.006) fat compared with the women on the Lo PRO diet, whereas, in men, there was no difference in fat loss between diets (3.9 vs. 5.1 kg)	LDL-C reduction was significantly greater on the High PRO diet (5.7%) than on the Low PRO diet (2.7%), p<0.01. TC decreased more on the High PRO diet (7%) than the low PRO diet (<1%), p<0.01. TG decreased significantly in both groups (high PRO, 17% and low PRO, 11%), p<0.001. There was no effect of time or diet for HDL-C.

Farnsworth et al., 2003 ³⁴⁸	16 weeks; 12 week energy restriction, 4 weeks energy balance	N=57 overweight males and females with elevated fasting insulin levels Mean BMI=34	Parallel arm; High PRO (27% PRO, 44% CHO, and 29% fat) or a standard PRO diet (16% PRO, 57% CHO, and 27% fat)	NSD between groups: -7.9 kg for both groups. Total fat loss (6.9 kg) did not differ between diet groups. In women, total lean mass was significantly (p=0.02) better preserved with the High PRO diet than with the Low PRO diet	Overall, TC decreased in both groups by 10.0% at wk 12 and by 5.3% at wk 16 (p<0.0001), with no effect of diet. LDL-C decreased by 12% at wk 12 and 6% at wk 16 (p<0.0001), with no effect of diet. HDL-C increased by 2% at week 12 and 5% by week 16 (p=0.001), with no effect of diet. A time-by-diet effect was observed (p<0.05) for TG- the decrease was 29% at wk 12, 23% at wk 16 for the HP diet, but only 12% (wk 12) and 10% (wk 16) with the LP diet.
Weight Loss Studies UP TO 6 MONTHS Which Resulted in No Change in LDL-C Levels					
Boden et al., 2005 ³⁴⁹	14 days	N=10 obese diabetic male and females Mean BMI=40	Cross-over; usual diet (7 days) followed by LCD (7 days; 21 g CHO/day)	SD: - 2 kg; p=0.042	Comparisons of mean serum levels before and after the LCD showed that TG levels decreased by 35% from 163 mg/dL to 105 mg/dL (P < 0.001) and that TC levels decreased by 10% from 180 mg/dL to 163 mg/dL (P < 0.02). There were no changes in LDL-C: 101 mg/dL following usual diet vs. 99 mg/dL following LCD, and HDL-C levels: 45 mg/dL following the usual diet vs. 44 mg/dL following the LCD.
Samaha et al., 2003 ³⁵⁰	6 months	N=79; severely obese males and females Mean BMI=43	Parallel arm: LCD (\leq 30 g/day) vs. LFD (<30% kcal from fat and 500 kcal deficit)	SD between groups: -5.8 kg (LCD) vs. -1.9 kg (LFD); p=0.002	TC, LDL-C, HDL-C levels did not change significantly during the six-month study within or between groups. However, there was a greater decrease in the mean TG level in the low-carbohydrate group than in the low-fat group (-38 mg/dL vs. -7 mg/dL, p=0.001).
Yancy et al., 2005 ³⁵¹	16 weeks	N=21 males (20) and females (1) with T2DM Mean BMI=42.2	Pre-post: Before and after LCD (<20 g CHO/day)	SD: -8.7 kg; p<0.001	Serum TG levels decreased 42% from 238 mg/dL to 139 mg/dL (p<0.001). Increases occurred in both HDL-C (+3 mg/dL) and LDL-C (+10 mg/dL) but these changes did not reach significance. TC did not change significantly.

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Table 11 (continued)

Reference	Study Duration	Subjects	Study design; Intervention Groups	Body Weight/ Body Fat	Other Parameters
Westman et al., 2008 ³⁵²	24 weeks	N=84 males and females with obesity and T2DM; 49 completed study Mean BMI=38	Parallel arm; LCD (<20 g CHO/d) vs. low glycemic index, reduced calorie diet (500 kcal deficit)	SD between groups: -11.1 kg (LCD) vs. -6.9 kg (Low glycemic), p=0.008	HDL-C: +5.6 mg/dL (LCD) vs. 0 mg/dL (low glycemic index, reduced calorie diet), p<0.01. Within group change from baseline (LCD group only): TG decreased from 210 to 143 mg/dL, p<0.05. There were no significant changes in TC or LDL-C in either group.
Daley et al., 2006 ³⁵³	3 months	N=102; obese males and females with poorly controlled T2DM Mean BMI=36	Parallel arm: LCD (70 g/d) vs. LFD (UK nutritional recommendations of <35% fat)	SD between groups: -3.6 kg (LCD) vs. -0.9 kg (LFD); p=0.001	Total cholesterol:HDL ratio improved; -0.48 (LCD) vs. -0.10 (LFD); p=0.01.
Dyson et al., 2007 ³⁵⁴	3 months followed by a 2 year follow-up	N=26 males and females; 13 with T2DM and 13 without; 22 completed the study; BMI=35	Parallel arm; LCD (<40 g CHO) vs. healthy eating (Diabetes UK nutritional recommendations)	SD between groups: -6.9 kg (LCD) vs. -2.1 kg (healthy eating), p=0.003 At the 2 yr follow-up no significant difference in wt loss between groups – both groups had returned to BL	No significant differences between or within group changes in lipids. No lipid data reported at the 2 yr follow-up.
Brehm et al., 2003 ³⁵⁵	3 and 6 month assessments	N=53 overweight/ obese women Mean BMI=33.5	Parallel arm; LCD (20 g/day for first two weeks, then increased to 40-60 g/d); LFD (max 30% kcal from fat and energy restricted)	SD between groups: -8.5 kg (LCD) vs. 3.9 kg (LFD); p<0.001	Significant time effects (p<0.01) for all lipids indicated that the subjects improved their lipid profiles at 3 months. However, by 6 months only the increase in HDL-C remained significant (+ 7 mg/dL and +4 mg/dL) for the LCD and LFD groups respectively. No significant changes were sustained for TC, LDL-C or TG at 6 mos.

Ebbeling et al., 2012 ²¹⁷	16 weeks	N=32 overweight or obese males and females ; 21 completed all phases Mean BMI=34.4	3-way cross-over study with 4 week treatment periods after an initial weight loss of 10 to 15% on a standard low-calorie diet. The diets were: 1) low-fat diet with high glycemic load and 60% CHO; 2) low-glycemic diet with moderate glycemic load and 40% CHO; LCD with low glycemic load and 10% CHO	No change – wt maintenance	Comparing the low-fat, low-glycemic index, and very low-carbohydrate diets, serum HDL-C (mean 40 mg/dL; 45 mg/dL; and 48 mg/dL, respectively; overall p<0.001), TGs (107 mg/dL; 87 mg/dL; and 66 mg/dL, respectively; overall p<0.001) was most favorable for the very low carb diet and least favorable with the low fat diet. LDL-C not reported.
Volek et al., 2009 ³⁵⁶	12 weeks	N=40 overweight males and females with atherogenic dyslipidemia Mean BMI=33	Parallel arm; LCD (~45 g CHO) vs. LFD (24% FAT), both hypocaloric diets (~1500 kcal)	SD between groups: -10.1 kg (LCD) vs. -5.2 (LFD)	LCD showed more favorable responses in TG (-51 vs. -19%); HDL-C (+13 vs. -1%), p<0.001; TC:HDL-C (-14 vs. -4%). LDL-C increased slightly on the LCD and decreased slightly on the LFD but there were no significant between or within group differences.
Brehm et al., 2005 ³⁵⁷	4 months	N=50 healthy, moderately obese females Mean BMI=33	Parallel arm; ad libitum LCD (20g CHO/d for 2 wks followed by an increase to 40-60 g if remained in ketosis) vs. energy restricted LFD (55% CHO, 15% PRO, 30% FAT)	SD between groups: -9.79 (LCD) vs. -6.14 kg (LFD); p<0.05) SD in body fat -6.20 (LCD) vs. -3.23 kg (LFD); p<0.05)	Significant time effects (p<0.05) were noted for TG (-48 mg/dL and -15 mg/dL), TC (-5 mg/dL and -7 mg/dL) and HDL-C (+7 mg/dL and +2 mg/dL) for the low carbohydrate and low fat diets, respectively. In addition, HDL-C increased significantly more on the low carb diet compared to the low fat diet (p<0.001). There were no changes in LDL-C in either group.
Yancy et al., 2004 ³⁵⁸	6 months	N=120 overweight, hyperlipidemic males and females (79 completed) Mean BMI=34.5	Parallel arm: ad libitum LCD (<20 g CHO/day with nutritional supplements) or energy-restricted LFD (<30% kcals from fat; 500 to 1,000 kcal restriction)	SD between groups at 24 weeks -12.9% (LCD) vs. 6.7% (LFD), p<0.001	LCD had greater decreases in TG [change: -74.2mg/dL vs. -27.9mg/dL; p=0.004] and greater increases in HDL-C levels [5.5mg/dL vs. -1.6mg/dL; p<0.001]. Changes in LDL-C levels did not differ statistically [1.6mg/dL] with the LCD and [-7.4mg/dL] with the low-fat diet; p=0.2.

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Table 11 (continued)

Reference	Study Duration	Subjects	Study design; Intervention Groups	Body Weight/ Body Fat	Other Parameters
Johnston et al., 2006 ³⁵⁹	6 weeks	N=20 males and females Mean BMI=35	Parallel arm; Ketogenic LCD (5% energy as CHO) vs. nonketogenic LCD (40% energy as CHO)	NSD between groups; -6.3 kg (KLCD) vs. -7.2 kg (NKLCD)	Compared with baseline, LDL-C concentrations increased in 5 KLCD dieters (0.08, 0.13, 0.41, 0.44, and 0.52 mmol/L, respectively) and decreased in the remaining 4 KLCD dieters (0.57 ± 0.18 mmol/L). In comparison, LDL-C increased in 2 NKLCD dieters (0.05 and 0.13 mmol/L) and decreased in the remaining 8 NLCD dieters (0.78 ± 0.21 mmol/L). HDL-C levels fell 9% in both diet groups.
McLaughlin et al., 2007 ³⁶⁰	16 weeks	N=29 male and female patients with T2DM Mean BMI=31	Parallel arm; LCD (40% CHO) vs. HCD (60% CHO) energy deficit of 750 kcal for both groups followed by a 2 wk maintenance phase	NSD between groups: -7.0 kg (HCD) vs. -5.9 (LCD)	Both groups experienced significant decreases in TG (29% and 21% for the HCD and LCD respectively). There were no significant differences between or within group differences in TC, HDL-C, LDL-C and LDL particle size in either group.
McLaughlin et al., 2006 ³⁶¹	16 weeks	N=57 insulin resistant, obese males and females Mean BMI=33	Parallel arm; LCD (40% CHO) vs. HCD (60% CHO), both calorie restricted diets	NSD between groups: -6.9 kg (LCD) vs. -5.7 kg (HCD); within groups difference p<0.001	Subjects on the LCD had greater reductions in fasting TG (0.53 mmol/L; p=0.04), greater increases in HDL-C (0.12 mmol/L; p<0.01) and LDL particle size (1.82 s; p<0.05), and a greater decrease in plasma E-selectin (5.6 ng/L; p=0.02) than subjects following the HCD. There was an increase in LDL-C in the low carb diet group.
Weight Loss Studies GREATER THAN 6 MONTHS Which Resulted in DECREASED LDL-C Levels					
Sacks et al., 2009 ²¹⁵	2 years	N=811 overweight males and females Mean BMI=33	Parallel arm; Random assignment to one of four diets (Fat/Pro/CHO): -20, 15, 65 -20, 25, 55 -40, 15, 45 -40, 25, 35	NSD between groups: At 6 months all groups lost an avg of 6 kg. Weight regain began at ~ 12 months. Weight loss remained similar at 2 years	At 2 years, the two low-fat diets and the highest-carbohydrate diet decreased LDL-C levels more than did the high-fat diets or the lowest-carbohydrate diet (low-fat vs. high-fat, 5% vs. 1% [p=0.001]; highest-carbohydrate vs. lowest-carbohydrate, 6% vs. 1% [p=0.01]). The lowest-carbohydrate diet increased HDL-C levels more than the highest-carbohydrate diet (9% vs. 6%, p=0.02). All the diets decreased TG levels similarly, by 12 to 17%.

Dansinger et al., 2005 ²¹¹	2, 6 and 12 months	N=160 overweight or obese males and females with known HTN, dyslipidemia, or hyperglycemia Mean BMI=35	Parallel arm; Atkins LCD (< 20g CHO, with a gradual increase to 50 g); Zone diet (40-30-30, CHO-FAT-PRO); Weight Watchers (24-32 points) and Ornish LFD (10% fat)	NSD between groups at any point	Comparing the Atkins, Zone Weight Watchers and Ornish Diets: all diets decreased LDL-C significantly with the exception of the Atkins diet (-13.5 mg/dL, -18.1 mg/dL, -14.2 mg/dL, and -25.2 mg/dL). All diets increased HDL-C significantly except Ornish (6.4 mg/dL, 5.1 mg/dL, 5.2 mg/dL, and -1.1 mg/dL, respectively). Only Weight Watchers and Ornish decreased TC significantly at 12 mos. (-8.1 mg/dL, -15.6 mg/dL, -12.6 mg/dL, -21.5 mg/dL).
Look AHEAD Research Group ³⁶²	12 months	N=2496 overweight individuals with T2DM Mean BMI=36	Intensive Lifestyle Intervention: A maximum of 30% of calories from fat (with a maximum of 10% of SFA) and a minimum of 15% from protein. Participants were prescribed portion controlled diets, which included the use of liquid meal replacements (provided free of charge) and frozen food entrees, as well as structured meal plans (comprised of conventional foods) for those who declined the meal replacements. Monthly reviews took place at an individual session to reassess progress	-8.6% body weight	Significant parameters: ↓ - LDL-C (-5.2 mg/dL), TG (-30.3 mg/dL), SBP (-6.8 mmHg), DBP (-3.0 mmHg) ↑ HDL- C (+3.4 mg/dL)
Wing et al., 2010 ³⁶³ Look AHEAD	4 years	N=2419	See above	-6.15% initial body weight	Significant parameters: ↓ LDL-C (-8.75 mg/dL), TG (-25.6 mg/dL), SBP (-5.3 mmHg), DBP (-2.9 mmHg) ↑ HDL- C (+3.7 mg/dL) <i>(continued on next page)</i>

Table 11 (continued)

Reference	Study Duration	Subjects	Study design; Intervention Groups	Body Weight/ Body Fat	Other Parameters
Barnard et al., 2009 ³⁶⁴	74 weeks	N=99 individuals with T2DM Mean BMI=35	Free living: The prescribed vegan diet (10% fat, 15% PRO, 75% CHO) consisted of vegetables, fruit, grains, and legumes. The conventional diet (15–20% PRO, 7% SFA, 60–70% CHO and monounsaturated fatty acids (MUFA); cholesterol < 200 mg/d) was individualized, based on body weight and plasma lipid concentrations, following 2003 ADA guidelines. Participants in the conventional group with a BMI >25 (all but 3) were prescribed energy deficits of 500–1000 kcal	Weight loss was significant within each diet group but not significantly different between groups (-4.4 kg in the vegan group and -3.0 kg in the conventional diet group, p=0.25)	In analyses before alterations in lipid-lowering medications, total cholesterol decreased by 20.4 and 6.8 mg/dL in the vegan and conventional diet groups, respectively (p=0.01); LDL-C decreased by 13.5 and 3.4 mg/dL in the vegan and conventional groups, respectively (p=0.03). HDL-C decreased in both groups (0.9 mg/dL and 0.7 mg/dL) in the vegan and conventional groups respectively.
Brinkworth et al., 2004 ³⁶⁵	64 weeks	N=66 obese patients with T2DM Mean BMI=34	Parallel arm: low-PRO (15% PRO, 55% CHO) or high-PRO diet (30% PRO, 40% CHO) for 8 weeks of energy restriction (~6.7 MJ/day) and 4 weeks of energy balance. Subjects were asked to maintain the same dietary pattern for a 12 month follow-up where no food was provided.	Weight reductions against baseline were -2.2±1.1 kg (low PRO) and -3.7±1.0 kg (high PRO), p<0.01, with no diet effect. Fat mass was not different from baseline in either group	TC, TG and LDL-C were significantly reduced in both diet groups (Low PRO: -8.8 mg/dL, -7.7 mg/dL and -11.6 mg/dL; Hi PRO: -44.3 mg/dL, -15.4 mg/dL and -7.7 mg/dL) following the 16 wk wt loss phase, however this decrease was not sustained during the 12 month follow-up period. In contrast, HDL-C remained stable during wt loss and increased 15% by both groups during the 12 month follow-up.

Jenkins et al., 2011 ²¹⁴ Portfolio Diet	6 months	N=351 patients with hyperlipidemia Mean BMI=27	Parallel arm: Low SFA diet (control) vs. dietary portfolio for which counseling was delivered at different frequencies that emphasized dietary incorporation of plant sterols, nuts, soy protein, and viscous fibers. The control dietary advice focused on low-fat dairy and whole grain cereals with fruit and vegetables and avoidance of specific portfolio foods	Participants in all groups experienced similar weight loss ($p<0.05$)	The LDL-C reductions from an overall mean of 171 mg/dL were -13.8% (95% CI, -17.2% to -10.3%; $p<0.001$) or -26 mg/dL (95% CI, -31 to -21 mg/dL; $p<0.001$) for the intensive dietary portfolio; -13.1% (95% CI, -16.7% to -9.5%; $p<0.001$) or -24 mg/dL (95% CI, -30 to -19 mg/dL; $p<0.001$) for the routine dietary portfolio; and -3.0% (95% CI, -6.1% to 0.1%; $p=0.06$) or -8 mg/dL (95% CI, -13 to -3 mg/dL; $p=0.002$) for the control diet. Percentage LDL-C reductions for each dietary portfolio were significantly more than the control diet ($p<0.001$, respectively). The 2 dietary portfolio interventions did not differ significantly ($p=0.66$). Both portfolio diet interventions decreased TC significantly (~10%) from baseline. There were no significant changes in HDL-C or TG for any group.
Ma et al., 2008 ³⁶⁶	12 months	N=40 individuals with T2DM Mean BMI=36	Parallel arm: ADA diet (goal CHO intake 55%) vs. Low GI diet (patients were educated on how to choose predominately low-GI foods). Both groups received monthly visits for 6 months with 2 visits in the next 6 months.	No significant difference in weight from baseline to 12 months for either group	TC levels were significantly decreased for both groups (ADA: -11mg/dL, Low GI: -15 mg/dL) at 6 months. However at 12 months. the ADA group decreased further for a total reduction of 18 mg/dL; whereas the Low GI group began trending upward with a total reduction of 2 mg/dL. HDL-C and TG levels were unchanged, and there was no difference between the two groups. However, there was a difference in LDL-C levels between the two groups at 12 months ($p=0.048$). At 12 months, LDL-C levels were significantly higher in the low-GI group than in the ADA group, with LDL-C levels decreasing by 17 mg/dL in the ADA group and increasing by 1.3 mg/dL in the low-GI group.

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Table 11 (continued)

Reference	Study Duration	Subjects	Study design; Intervention Groups	Body Weight/ Body Fat	Other Parameters
Rock et al., 2010 ³⁶⁷	2 years	N=441 overweight and obese women Mean BMI=34	Parallel arm: center based and telephone groups received free pre-packaged prepared foods (following a low fat 20-30% fat, reduced energy diet) interactions with staff and one-to-one contacts with a counselor. Usual care group received two sessions with a staff dietitian who provided written materials and encouraged a 500 to 1000 kcal deficit per day	Weight data were available at 24 months for 407 women. Mean weight loss was 7.4 kg for the center-based group, 6.2 kg for the telephone-based group, and 2.0 kg for the usual care control group after 24 mo. ($p < 0.001$ for intervention effect)	From baseline to 12 months Usual Care: Significant reductions in TC (-14 mg/dL), LDL-C (-8 mg/dL), and HDL-C (-3 mg/dL) Center based and telephone based: no significant changes.
Foster et al., 2010 ³⁶⁸	2 years	N=307 overweight/ obese males and females Mean BMI=36	Parallel arm: LCD (<20 g/d for 3 mo followed by a 5 g increase per week until desired weight achieved); LFD reduced energy intake and <30% kcal from fat. Both diets were combined with a comprehensive behavioral treatment program	NSD between groups: Weight loss was 11 kg at year 1 and 7 kg at 2 years.	There was a significant effect of time for the decrease in LDL-C across both groups. However the decrease was significantly greater at 3 and 6 months in the low-fat group (-6.36 mg/dL and -9.52 mg/dL) than in the low-CHO group (+7.2 mg/dL and 0.54 mg/dL), but this difference (between groups) did not persist at 12 mos. (low fat: -8.66 mg/dL; Low-CHO: -8.57 mg/dL) or 24 months (Low fat: -8.01 mg/dL; Low-CHO: -4.78 mg/dL). Decreases in TG levels were greater in the low-CHO than in the low-fat group at 3 months. (-40.0 mg/dL vs. -17.99 mg/dL) and 6 months (-40.06 mg/dL vs. -24.30 mg/dL) but not at 12 (-31.52 mg/dL vs. -17.92 mg/dL) or 24 months (-12.19 mg/dL vs. -14.58 mg/dL). Increases in HDL-C levels were significantly greater in the low-CHO than in the low-fat group at 3 (2.30 mg/dL vs. -0.47 mg/dL), 6 (6.21 mg/dL vs. 0.89 mg/dL), 12 (7.96 mg/dL vs. 3.94 mg/dL) and 24 months (7.75 mg/dL vs. 4.64 mg/dL).

Weight Loss GREATER THAN 6 MONTHS Which Resulted in No Change in LDL-C Levels**Shai et al., 2008²¹⁶**

2 years

N=322 moderately obese males and females
Mean BMI=31

Parallel arm; LFD (30% FAT, calorie restricted), Mediterranean type MFD (35% FAT from extra virgin olive oil and nuts, calorie restricted), LCD (20 g CHO for 2 mo., then increased to 120 g for wt main., calories were not restricted)

NSD between groups:
Max weight loss occurred from month 1 to 6 – reductions were greatest in the LCD and MFD groups, $p<0.001$.
At 24 mo mean wt loss for the LFD group was 2.9 kg, 4.4 kg for MFD, and 4.7 kg for LCD, $p<0.001$ HDL-C increased during the weight loss and maintenance phases in all groups, with the greatest increase in the low-carbohydrate group (8.4 mg/dL $p<0.01$ for the interaction between diet group and time), as compared with the low-fat group (6.3 mg/dL). TG levels decreased significantly in the low-carbohydrate group (23.7 mg/dL, $p=0.03$ for the interaction between diet group and time), as compared with the low-fat group (2.7 mg/dL). LDL-C levels did not change significantly within groups, and there were no significant differences between the groups in the amount of change. Overall, the ratio of TC to HDL-C decreased during both the weight-loss and the maintenance phases. The low-carbohydrate group had the greatest improvement, with a relative decrease of 20% ($p=0.01$ for the interaction between diet group and time), as compared with a decrease of 12% in the low-fat group.**Stern et al., 2004²¹⁹**

12 months

N=132 obese males and females
Mean BMI=43

Parallel arm; LCD (< 30 g/day) vs. LFD (<30% kcal from fat and 500 kcal/day deficit)

NSD between groups:
-5.1 kg (LCD) vs. -3.1 kg (LFD)There were no significant between or within group changes for TC or LDL-C. TG levels decreased significantly more in the LCD group (-58 mg/dL) compared to the LFD (+4 mg/dL), $p<0.05$. The mean HDL-C decreased more in the LFD group (-5 mg/dL) compared to the LCD (-1 mg/dL), $p<0.05$.**Davis et al., 2009²¹⁸**

1 year

N=105 overweight males and females with T2DM
Mean BMI=36

Parallel arm: LCD (20-25 g CHO for 2 weeks followed by a 5 g increase each week) vs. LFD (25% FAT)

NSD between groups: At 3 months LCD lost an avg of 1.7 kg/mo vs. 1.2 kg/month for the LFD. By 1 yr both groups had a 3.4% body weight reduction

Over 12 months there were no significant changes in TC, TG, or LDL-C for either group. There was a significant increase in HDL-C in the LCD group (+6 mg/dL) which occurred at 6 months and was sustained at 12 months.

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Table 11 (continued)

Reference	Study Duration	Subjects	Study design; Intervention Groups	Body Weight/ Body Fat	Other Parameters
Brinkworth et al., 2009 ³⁶⁹	8 weeks	N=121 overweight or obese males and females with abdominal obesity and one other risk factor of metabolic syndrome; 91 completed the study. Mean BMI=34	Parallel arm: LCD (4% CHO) vs. LFD (30% fat) isoenergetic diets with energy restriction of 30%	SD between groups: -7.8 kg (LCD) vs. -6.4 kg (LFD), p=0.04.	Markers of bowel function.
	1 year follow-up	N=118 participants from previous study; 69 completed this trial		NSD between groups: -14.5 kg (LCD) vs. -11. Kg (LFD)	Compared with the LF group, the LC group had greater decreases in TG (-0.58 vs. -0.22mmol/L; p= 0.011), increases in HDL-C (0.30 vs. 0.07mmol/L; p=0.018) and LDL-C (0.6 vs. 0.1mmol/L; p=0.001).
Foster et al., 2003 ²¹²	3, 6, and 12 month assessments	N=63 obese men and women. Mean BMI=34	Parallel arm; LCD (max 20 g/d for first 2 wks then gradual increase until desired weight stabilized. LFD (25% kcal from fat, energy restricted)	SD between groups: 3 months -6.8 (LCD) vs. -2.7 % (LFD) of body weight; p=0.001) and 6 months -7.0 (LCD) vs. -3.2 % (LFD) of body weight, p=0.02), the difference at 12 months was NS	There were no significant between or within group differences in TC or LDL-C (at 12 months) There was a significantly greater increase in HDL-C in the LCD (18.2 %) compared to the LFD (3.1%). In addition, there was a greater decrease in TG in the LCD (-28%) compared to the LFD (+1.4 %).
Gardner et al., 2007 ²¹³	12 months	N=311 overweight/obese non-diabetic, premenopausal females Mean BMI=32	Parallel arm; Atkins LCD (20 g/d or less CHO for 2-3 months followed by increase to 50 g/d), Ornish diet (no more than 10% calories from fat), LEARN diet (prudent diet of 55-60% CHO and less than 10% SFA), and the Zone diet (40-30-30 distribution of CHO, PRO, and fat)	Mean 12-month weight loss was significantly different between the Atkins and Zone diets (p<.05). Mean 12-month weight loss was as follows: Atkins, -4.7 kg ; Zone, -1.6 kg; LEARN, -2.6 kg; and Ornish, -2.2 kg. Wt loss was not statistically different among the Zone, LEARN, and Ornish groups	At 12 months there were no significant changes in LDL-C for any of the diets. At 2 months only the Learn and Ornish diet produced significant reductions in LDL-C (-7.3 mg/dL and -10.1 mg/dL, respectively). All groups with the exception of Ornish increased HDL-C (Atkins 4.9 mg/dL, Zone 2.2 mg./dL, LEARN 2.8 mg/dL, and Ornish 0.0 mg/dL). All groups lowered TG with the greatest reduction in the Atkins group (-29.3 mg/dL), Zone -4.2 mg/dL, LEARN -14.6 mg/dL, and Ornish -14.9 mg/dL.

Brehm et al., 2009 ³⁷⁰	12 months	N=124, overweight / obese with T2DM Mean BMI=36	Parallel arm: high-MUFA diet (45% CHO, 15% PRO, 40% fat, 20% MUFA) vs. high-CHO diet (60% CHO, 15% PRO, 25% fat); similar SFA in both diets. 200-300 calorie deficit for both groups	NSD between groups; within group differences only: -4.0 kg (MUFA) vs. -3.8 kg (CHO)	There were no between or within group differences for TC, TG, or LDL-C. Both groups experienced a significant (5 mg/dL) increase in HDL-C.
Li et al., 2005 ³⁷¹	12 months	N=104 patients with T2DM; 77 completed the trial Mean BMI=33	Parallel arm: soy-based meal replacement (MR) plan vs. an individualized diet plan (IDP; as recommended by the American Diabetes Association)	Percentage weight loss in MR group (4.57+/-0.81%) was significantly greater (p<0.05) than in IDP group (2.25+/-0.72%)	There were no significant differences between treatment groups at any time point for TC, TG, LDL-C, and HDL-C. However, the MR group maintained a decrease in TG (-28 mg/dL) from baseline to 12 months (p<0.03).
Cheskin et al., 2008 ³⁷²	Weight loss at 34 weeks; weight maintenance at 86 weeks	N=119 overweight/ obese men and women with T2DM; 48 completed the 34 wk phase and 24 completed the 86 weeks Mean BMI=35	Parallel arm: Standard diet (SD): 25% energy deficit diet in accordance with ADA recommendations vs. a 25% deficit portion controlled diet (PCD) in which 50-60% of the calories were from meal replacements. Nutrient composition for both: 45-50% CHO, 25-30% fat, 15-25% PRO	After the 34-week active phase, weight loss among completers was 6.84% (7.3 ± 6.2 kg) on the PCD versus 3.70% (3.7 ± 3.2 kg) on the SD (p=0.39). At 86 weeks, completers of both groups maintained significant weight loss; however, there was no significant between-group difference	At 34 weeks there were no significant changes in TC or LDL-C. However, HDL-C levels were significantly increased in both the PCD (9.1%) and SD (6.7%) groups. The increase was maintained at 86 weeks. At 34 weeks, the PCD group reduced TG 19.4% (p< 0.0001), whereas the SD group showed no change. However, the between-group difference was not significant. At 86 weeks, there were no significant within- or between-group differences.

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Table 11 (continued)

Reference	Study Duration	Subjects	Study design; Intervention Groups	Body Weight/ Body Fat	Other Parameters
Richard et al., 2012 ³⁷³	9 months	N=19 males Mean BMI=33.4	The subjects' diet was first standardized to a baseline North American control diet that they consumed for 5 weeks under isoenergetic, weight maintaining conditions. The participants then consumed the MedDiet for 5 weeks under isoenergetic, weight-maintaining conditions. This first part of the study was controlled feeding. Next was a 20-week weight-loss period in free-living conditions during which they were given advice on how to create a 500 kcal deficit in their daily energy intake. Lastly, the subjects consumed the MedDiet for the second time for 5 weeks under controlled feeding, weight-stabilizing conditions	After 20 weeks energy restriction and 5 weeks stabilization body weight decreased 10.2% and waist circumference by 8.6 cm compared with baseline measures (after control diet)	The MedDiet in the absence of weight loss significantly reduced plasma total cholesterol (-7.8%), LDL-C (-9.9%) and LDL-apo B (-10.4 %) compared with the control diet (all p<01). Combining weight loss with the MedDiet had no further impact on TC or LDL-C.

Ratner et al., 2006 ³⁷⁴	3 years	N=3234 individuals with IGT Mean BMI=34	Parallel arm: intensive lifestyle group designed to achieve and maintain a weight reduction of at least 7% of initial body weight through consumption of a healthy low calorie, low-fat diet and to engage in physical activity; metformin group and the placebo group	Did not report	Over the 3 year period, there were no statistical differences among the placebo, metformin, and intensive lifestyle groups in the overall mean % change from baseline in either TC level (-1.2% vs. -0.9% vs. -2.3%, respectively) or LDL-C level (-1.3% vs. -0.3% vs. -0.7%, respectively). TG levels fell in all groups, but fell significantly more in the intensive lifestyle group (-25.4 mg/dL) than in the placebo (-11.9 mg/dL) and metformin (-7.4 mg/dL) groups. HDL-C level significantly increased in the lifestyle group (1.0 mg/dL) compared with the metformin (0.3 mg/dL) and placebo (0.1 mg/dL) groups. Furthermore, intensive lifestyle favorably altered the LDL phenotype with a reduction in the prevalence of phenotype B representing a smaller, denser, more atherogenic LDL particle ($p < 0.001$ compared with both placebo and metformin).
Esposito et al., 2009 ³⁷⁵	4 years	N= 215 overweight males and females with newly diagnosed T2DM Mean BMI=30	Parallel arm; Mediterranean style diet (<30% CHO) vs. LFD (<30% FAT)	Participants in both groups lost weight at year 1 but the reductions were greater in the Med group. The between group differences were attenuated in the 2 nd yr and there were no differences by years 3 and 4	Participants in the Med group had significantly greater increase in HDL-C (3.4 mg/dL) compared to the LFD group (<0.1 mg/dL) and greater decrease in TG (-24.8 mg/dL) compared to the LFD (-6.2 mg/dL). TC also decreased more in the Med group (-10 mg/dL) compared to the LFD (-4 mg/dL) but the difference was only significant for the first 2 years. No LDL-C data reported.

Exercise programs have also been shown to decrease fasting TGs by 4% to 37% (approximate mean change of 24%).²⁴⁶ The authors of one recent study found that treadmill walking-induced reductions in VLDL₁ (large VLDL particles) concentrations are mediated by increased catabolism rather than reduced production, which may be facilitated by compositional changes to VLDL₁ particles that increase their affinity for clearance from the circulation.²⁴⁷

Exercise training can favorably alter lipids and lipoproteins independent of significant body weight changes (particularly when assessing lipoprotein particle number changes).^{241,248} Moderate volumes and intensities (eg, walking ~12 miles per week at 40%–55% of aerobic capacity) can significantly reduce NMR spectrometry-measured LDL-particle number when total cholesterol and Friedewald-predicted LDL-C remained essentially unchanged. Such patients on a return clinic visit would be considered unresponsive to exercise therapy when a conventional lipid profile was used to score the patient's progress.²⁴¹

Inactivity and lipids

A modest amount of exercise training can prevent a deterioration of the lipid profile that is seen with inactivity.²⁴⁹ This is particularly true for LDL and HDL size, LDL particle number, and total HDL-C. In fact, it appears that only 7 to 10 miles of walking per week will prevent inactivity-associated deterioration in these lipid parameters.²⁴⁹ Moderate-intensity but not vigorous-intensity aerobic exercise of sufficient quantity can illicit sustained reductions in VLDL-TG over several weeks of days of de-training ($P < .05$).²⁴⁹

Current guidelines for physical activity, weight loss, and dyslipidemia

The American College of Sports Medicine (ACSM) guidelines on physical activity and weight loss in overweight and obese adults state that these individuals should eventually progress to greater amounts of exercise (eg, 250–300 min/week or ≥ 2000 kcal/week of leisure-time physical activity). This volume may be accumulated with repeated exercise bouts of ≥ 10 minutes. ACSM advises that such activity should be aerobic, 40–75% of aerobic capacity, for 5–7 days a week, for 30–60 minutes per day.²²³ For improvement in overall lipoprotein status (LDL-C, HDL-C, non-HDL-C, and TG levels) The ACSM recommends the same guidelines for energy expenditure, duration, and frequency of physical activity as advised for weight loss.²⁵⁰

A final word on physical activity and weight loss: looking at Look AHEAD

The Action for Health in Diabetes (Look AHEAD) study, a trial evaluating an intensive lifestyle-intervention

Table 12 Primary factors influencing exercise-generated weight loss and exercise training lipid/lipoprotein response

Exercise-generated weight loss
Daily energy balance
Dietary compensation, energy conservation
Energy expenditure of physical activity
Mode of exercise
Intensity and duration of exercise
Exercise economy
Postexercise metabolism
Changes in lean muscle protein and total body water
Metabolic phenotype and genotype (eg, no. of type I muscle fibers, perilipin haplotype)
Gender
Exercise training lipid/lipoprotein response
Total calories expended
Length of training period (eg, 1 month, 6 months, 18 months)
Corresponding body fat loss
Corresponding dietary changes
Concomitant alcohol intake
Baseline lipid values
Plasma volume changes
Menopausal status
Race/Ethnicity
Genetic factors (eg, apolipoprotein E isoforms)
Biologic variation (seasonal and diurnal changes)

Originally described by Boutcher and Dunn, 2009.³⁷⁶

program aimed at achieving and maintaining weight loss in patients with T2DM, was stopped early (October 19, 2012) at the 11-year point because of failing to achieve the primary end point: *CV death, nonfatal MI, and nonfatal stroke* compared with a “control” of diabetes control and education.²⁵¹ This trial did reach lifestyle goals and demonstrated significant reductions in most CVD risk factors but not LDL-C. The Look AHEAD trial incorporated an intensive diet and exercise program. Although this trial is undergoing intensive scrutiny, it is important to emphasize that the physical activity goal in the intensive lifestyle group was ≥ 175 minutes of moderate exercise per week plus daily lifestyle activity (note that was the goal—it remains to be seen what was actually achieved in the intensive lifestyle group). The ACSM consensus guidelines for exercise and weight loss is at least 200 minutes (preferably 250–300 minutes) of moderate level physical activity per week, underscoring that the weekly physical activity energy expenditure required to achieve weight loss is substantial.

Weight-management drug treatments

Historically, weight-management drugs have presented clinical challenges due to issues of safety and tolerability.²⁵² As a result, from the date of orlistat approval in 1999 through 2012, no new weight-management drugs had

received regulatory approval in the United States for over a decade for long-term treatment of increased adiposity. Nonetheless, even among older and withdrawn weight management drugs, the potential of such agents in improving health was supported by improvements in lipid levels, as well as improvement in other metabolic parameters.²⁵³

The rimonabant development program is illustrative of both the promise and the challenges in characterizing the interrelationship between adiposity and dyslipidemia. Rimonabant is a cannabinoid CB1 receptor antagonist that through an increase in satiety, reduced body weight. In 2008, rimonabant was withdrawn from the European market, and it was never approved in the United States as a therapeutic agent, mainly because of the onset of adverse psychiatric effects. During its extensive development, rimonabant was thought to have particular potential to not only reduce body weight, but also improve adipocyte and adipose tissue function because CB1 receptors were not only found in the brain, but also liver, pancreas, skeletal muscle, gastrointestinal tract, and adipocytes themselves. This suggested the possibility that the endocannabinoid system may have direct effects upon metabolic processes that may directly and/or indirectly affect fat function or dysfunction, and thus a potential therapeutic treatment target towards treating both adiposity and adiposopathy.²⁵⁴ Although it was not ultimately successful as a therapeutic weight-management agent, several messages can be drawn from the rimonabant data, as shown in Figure 18.

First, the reduction in body weight (Fig. 18A) and waist circumference (Fig. 18B) with rimonabant was associated with a reduction in TG levels (Fig. 18C) and increase in HDL-C levels (Fig. 18D). LDL-C levels did not decrease. Second, of note was the placebo group, which experienced marginal weight loss, which was associated with no change in TG levels, no decrease in LDL-C levels, and an increase in HDL-C levels (Fig. 19).

At the time of this writing, weight-management drugs approved for short-term (ie, 12-week) weight management include amphetamine-like agents (eg, diethylpropion and phendimetrazine), with the most commonly prescribed antiobesity agent being phentermine (Table 13).^{255,256} Weight-management agents approved for longer term use include orlistat (Table 14), lorcaserin (Table 15), and a controlled release combination of phentermine and topiramate (Tables 16 and 17). Finally, investigational weight-loss agents include a combination drug of naltrexone (Table 18) and bupropion (Table 19) and liraglutide (which is not discussed herein).¹³

General principles

Approximately 5% weight loss in overweight patients may reduce adipocyte size, improve adipocyte and adipose tissue functionality, and thus improve adiposopathic responses.²⁵⁷ This helps account for why “only” 5% to 10%

weight loss is often sufficient to improve metabolic disorders such as dyslipidemia.²⁵⁸ Mechanistically, orlistat is unique in that it impairs gastrointestinal fat absorption by inhibiting gastrointestinal lipase activity. Most other weight-management drugs promote a reduction in caloric intake through increased satiety. Little evidence supports weight-loss drugs as increasing overall metabolic rate, even with amphetamine use, which was previously approved as a weight management therapy.²⁵⁶

The arcuate nucleus of the hypothalamus is located in the portion of the central nervous system (CNS) responsible for desirous and responsive behaviors, such as fight, flight, feeding, and mating (Fig. 20). An increase in anorexigenic and decrease in orexigenic central nervous system signaling may help account for the catabolic (weight loss) effects of lorcaserin (serotonergic effects), phentermine (noradrenergic effects), topiramate (possibly leptin effects), naltrexone (opioid effects), and bupropion (noradrenergic effects) (see Tables 13–19).

Phentermine

The clinical development and different formulations of phentermine (Table 13) were previously reviewed.^{255,256} Phentermine was approved as a short-term (12-week) weight-management therapeutic agent in 1959 and is the most widely prescribed antiobesity agent.²⁵⁶ Largely resulting from the regulatory environment during the time of its approval, and its generic status (diminishing incentives for funding further research), data concerning the metabolic effects of phentermine are limited, with almost no existing phentermine monotherapy data on weight loss and metabolic effects for longer than 1 year. Nonetheless, in a 14-week placebo-controlled study (with 2 weeks being placebo run-in) of 68 relatively healthy overweight and obese Korean adults with BMI ≥ 25 kg/m² (mean BMI = 29 kg/m²), phentermine HCl 37.5 mg produced a significant 7.2-kg weight loss compared with 2 kg weight loss in the placebo group ($P < .001$) in the intent-to-treat analysis. In a “completer analysis” (analysis of only those completing the study) of a subset of 36 subjects, phentermine produced 7.5 kg of weight loss compared with 3 kg weight loss in the placebo group. In the phentermine and placebo groups, the baseline total cholesterol, TG, LDL-C levels, and HDL-C levels were 183 and 167 mg/dL, 120 and 148 mg/dL, 117 and 93 mg/dL, and 52 and 51 mg/dL, respectively. In the completer analysis, the mg/dL changes in these same respective phentermine and placebo lipid parameters were -7.8 mg/dL and +11 mg/dL; -31 mg/dL and +16 mg/dL; -1 mg/dL and +14 mg/dL; and +2 mg/dL and +3 mg/dL. The main adverse experiences were dry mouth and insomnia.

These results are limited by reflecting a completer analysis subset in Koreans, rather than an intent-to-treat analysis of a more diverse patient population. Nonetheless, relative to placebo in an overweight Asian population with

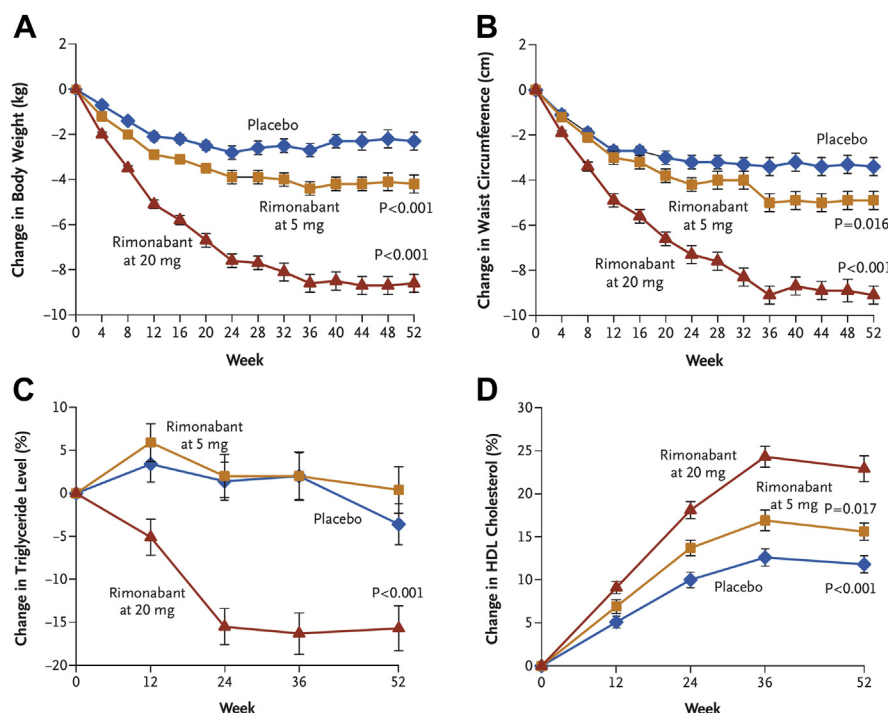


Figure 18 Effect of placebo or rimonabant for 52 weeks on body weight (A), waist circumference (B), plasma TG levels (C), and HDL cholesterol levels (D). Reproduced with permission.³⁸³

minimal to no dyslipidemia, and among those who took phentermine until study end, this study suggests phentermine therapy for 12 weeks might be expected to produce ~4.5 kg (~15%) of weight loss, ~20 mg/dL (~10%) decrease in total cholesterol, ~45 mg/dL reduction in TG (~35%), 15 mg/dL (~15%) reduction in LDL-C, and minimal change in HDL-C (~2%).²⁵⁹ The metabolic effects of weight management therapies are likely to be greater among patients who take the drugs as recommended (“completers”). In addition, the lipid parameter expected to most improve with weight loss are TG levels, to a degree that may approximate the effects of agents specifically indicated as TG lowering therapies.²⁶⁰

Orlistat

Orlistat (Table 14) was approved as a long-term weight management treatment in 1999. In a meta-analysis of 28 clinical trials of overweight patients treated with orlistat 120 mg three times per day for 1 year, the weighted mean weight loss was 3.9 kg among low-risk CVD patients, 2.5 kg among patients with T2DM, and 2.0 kg among patients at high risk for CVD.²⁶¹ In the low-risk CVD population, orlistat produced a placebo-corrected 12 mg/dL reduction in total cholesterol, 9.7 mg/dL reduction in LDL-C, 1.2 mg/dL reduction in HDL-C, and no change in TG levels. In the T2DM population, orlistat produced a placebo-corrected 14 mg/dL reduction in total cholesterol, 9.7 mg/dL reduction in LDL-C, 1.2 mg/dL reduction in HDL-C, and an 18 mg/dL reduction in TG levels. In the

high-risk CVD population, orlistat produced placebo-corrected 9.3 mg/dL reduction in total cholesterol, 7.3 mg/dL reduction in LDL-C, 0.78 mg/dL reduction in HDL-C, and a 9.7 mg/dL increase in TG levels. The overall clinical messages are that: (1) meta-analyses often report more modest lipid improvements in endpoints compared to selected clinical trials; (2) increases in HDL-C are sometimes difficult to achieve with weight loss interventions focused on reduced caloric intake (as opposed to negative caloric balance achieved through marked increased physical activity), with active weight loss often accompanied by transient decrease in HDL-C levels; and (3) weight loss with weight-management drug therapy may be more difficult among sicker patients, such as those with T2DM

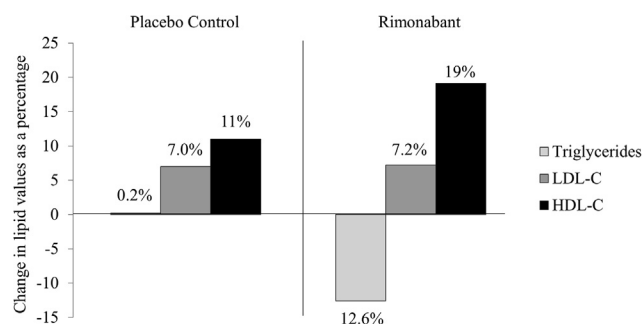


Figure 19 Percentage changes in lipoproteins after rimonabant 20 mg/day for 52 weeks. In this analysis, data contained the last observation carried forward with each parameter. Reproduced with permission.³⁸³

Table 13 Phentermine²⁵⁵

Class of agent	<ul style="list-style-type: none"> • Short-term (12-week) weight-management agent • DEA Schedule IV drug*
Mechanism/s of action	<ul style="list-style-type: none"> • Sympathomimetic amine related to amphetamine, but with minimal abuse potential • Noradrenergic effects • Minimal dopaminergic effects • Increase in satiety • No appreciable effect on energy expenditure
Potential adverse effects	<ul style="list-style-type: none"> • Palpitations • Tachycardia • Increase in blood pressure • Tremor • Diaphoresis • Overstimulation of the central nervous system (eg, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, psychosis) • Headache • Dry mouth • Unpleasant taste • Constipation • Urticaria • Impotence and changes in libido
Contraindications and cautionary use	<ul style="list-style-type: none"> • Unstable cardiovascular disease and dysrhythmias • Uncontrolled moderate to severe high blood pressure • Hyperthyroidism • Glaucoma • Agitated states • History of ongoing illicit drug or alcohol abuse • Pregnancy and nursing mothers
Potential drug interactions	<ul style="list-style-type: none"> • The use of phentermine with adrenergic agents that affect the central nervous system agents, such as decongestants, may increase blood pressure and pulse. • Phentermine may decrease the hypotensive effects of guanethidine. • Phentermine is sometimes described to interact with monoamine oxidase inhibitors, with the potential for hypertensive crisis and “serotonin syndrome.” However, a survey of bariatric physicians using sympathomimetic appetite suppressants and serotonin-selective reuptake inhibitors did not find any cases of serotonin syndrome among 1174 patients.³⁷⁷
Metabolism	<ul style="list-style-type: none"> • Phentermine is metabolized by the liver, with most (70%–80%) excreted by the kidney.
Administration	<ul style="list-style-type: none"> • Once a day in the morning. • May be best to avoid late evening administration to reduce the risk of insomnia.
Pregnancy	<ul style="list-style-type: none"> • Category X (changed from category C),[†] at least in part on the basis that weight loss offers no potential benefit to a pregnant woman and may result in fetal harm.

*In the United States, certain drugs are regulated under the Controlled Substances Act wherein “controlled substances” are assigned scheduling by the Drug Enforcement Agency. Schedule I controlled substances include drugs with a high potential for abuse and with no accepted medical use (eg, heroin, lysergic acid diethylamide [ie, LSD]). Drug Enforcement Agency Schedule II includes those with a high potential for abuse but with legitimate medical use (eg, topical cocaine, methadone, morphine, amphetamine). Schedule III drugs have less abuse potential than Schedule II and useful medical purposes (eg, some amphetamine-like drugs, some barbiturates). Schedule IV drugs have less abuse potential than Schedule I–III and useful medical purposes (phentermine, diazepam). Schedule V drugs have less abuse potential than Schedule I–V and useful medical purposes (eg, opioid derivatives used as anti-diarrheals and antitussives or cough medications with codeine).

†The Food and Drug Administration categorizes the risk of drugs during pregnancy. Category A = adequate human studies to support no fetal risk during pregnancy (eg, levothyroxine). Category B = no adequate studies in pregnant humans, but no adverse animal reproductive studies or adequate studies in pregnant humans do not support fetal risk, but animal studies do suggest fetal risk (eg, colesevelam HCl, prenatal vitamins, glucophage, some insulins, ondansetron, amoxicillin, acetaminophen). Category C = no adequate studies in pregnant humans, animal reproductive studies suggest fetal risk, but potential benefits in pregnant women may outweigh potential risks (eg, ezetimibe, extended-release niacin, fenofibrate, gemfibrozil, prescription omega-3 fatty acids, albuterol sertraline). Category D = human studies or marketing experiences provide evidence of fetal harm but potential benefits in pregnant women may outweigh potential risks (eg, doxycycline, lorazepam, paroxetine, phenytoin). Category X = human studies or marketing experiences provide evidence of fetal harm, and potential benefits to pregnant women do not outweigh potential risk (eg, weight-management drugs, statins and statin-containing combination lipid-altering drugs, temazepam, testosterone).

Table 14 Prescription orlistat summary³⁷⁸

Class of agent	<ul style="list-style-type: none"> • Weight management agent • No Drug Enforcement Agency scheduled listing (not a controlled substance)
Mechanism/s of action	<ul style="list-style-type: none"> • Reversible inhibitor of gastrointestinal lipase
Potential adverse effects	<ul style="list-style-type: none"> • Oily discharge from the rectum • Flatus with discharge • Fecal urgency fatty/oily stool, oily anal evacuation • Increased defecation • Fecal incontinence • May increase risk of cholelithiasis, particularly if weight loss is substantial • May increase risk of urinary oxalate, contributing to nephrolithiasis with rare reports of oxalate nephropathy, and renal failure • Rare postmarketing reports of severe liver injury with hepatocellular necrosis or acute hepatic failure resulting in liver transplantation or death
Contraindications and cautionary use	<ul style="list-style-type: none"> • Chronic malabsorption syndrome • Cholestasis • Pregnancy or nursing mothers
Potential drug interactions	<ul style="list-style-type: none"> • May decrease cyclosporine levels • May decrease fat-soluble vitamin absorption, with the recommendation that patients should take a daily multivitamins containing vitamins A, D, E, K, and beta carotene • May reduce levothyroxine levels • May enhance warfarin effect, if vitamin K absorption is diminished
Metabolism	<ul style="list-style-type: none"> • Although orlistat and its M1 and M3 metabolites may be subject to biliary excretion, 97% of orlistat excreted in feces, with 83% being unchanged orlistat
Administration	<ul style="list-style-type: none"> • One 120 mg capsule three times a day with each main meal containing fat (during or up to 1 hour after the meal) • Vitamin supplement should be taken at least 2 hours before or after the administration of orlistat, such as at bedtime • Cyclosporine should be administered 3 hour after orlistat • Levothyroxine and orlistat should be taken at least 4 hours apart
Pregnancy	<ul style="list-style-type: none"> • Orlistat is pregnancy category X (changed from category (B). Although no embryotoxicity or teratogenicity is reported in animals, orlistat is contraindicated during pregnancy on the basis that weight loss offers no potential benefit to a pregnant woman and may result in fetal harm.

or high-risk CVD. Given its unique mechanism of action, orlistat may have local metabolic effects beyond weight loss, which may help account for improvements in the reduction in circulating free fatty acid levels and insulin resistance.²⁶² Because of these differences in mechanism of action, the pattern of lipid effects with orlistat (ie, more robust reduction in LDL-C and less reduction in TG levels) may differ relative to other weight management agents.

Lorcaserin

Lorcaserin (Table 15) was approved as a weight-management agent in 2012. The three sentinel phase 3 lorcaserin trials included the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial,²⁶³ Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) trial,²⁶⁴ and the Behavioral Modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus (BLOOM-DM) trial.²⁶⁵ The lorcaserin-development program and the effects of lorcaserin on adiposopathy were previously reviewed.^{266,267}

As an illustrative example, the placebo-controlled BLOOM study evaluated lorcaserin 10 mg twice per day for 52 weeks in 3182 obese or overweight adults with mean BMI 36.2 kg/m² (this study also had a second phase extending an additional year, for a total of 2 years).²⁶³ The most frequent adverse events reported with lorcaserin were headache, dizziness, and nausea. After 1 year, the lorcaserin group lost an average of 5.8 kg compared with 2.2 kg with placebo ($P < .001$). For both groups, baseline lipid levels included total cholesterol ~195 mg/dL, LDL-C ~113 mg/dL, HDL-C 55 mg/dL and TGs 137 mg/dL. At 1 year, the percent changes in these respective lipid parameters in the lorcaserin versus the placebo group were -0.9% and +0.6% ($P = .001$), +2.9% and +4.0% ($P = .049$), +0.1% and -0.2% ($P = .72$), and -6.2% versus +0.1 ($P < .001$). In a patient population without substantial dyslipidemia, the net placebo-corrected 3-kg weight loss found with lorcaserin may produce statistically significant, albeit mild, reductions in total cholesterol and LDL-C, with a somewhat more robust (6%) reduction in TG levels. The reduction in TG levels based upon higher versus lower baseline TG levels (eg, tertile analysis) was not reported.

Table 15 Lorcaserin summary^{266,267,379}

Class of agent	<ul style="list-style-type: none"> • Weight management agent • Drug Enforcement Agency Schedule IV drug
Mechanism/s of action	<ul style="list-style-type: none"> • Serotonin (5-hydroxytryptamine) 2c receptor agonist, which may increase satiety • Little evidence to support increased energy expenditure
Potential adverse effects	<ul style="list-style-type: none"> • Headache • Dizziness • Fatigue • Nausea • Dry mouth • Constipation • Cough • Reduced heart rate • Hyperprolactinemia
Contraindications and cautionary use	<ul style="list-style-type: none"> • If signs or symptoms of valvular heart disease develop, then discontinuation of lorcaserin should be considered during evaluation for valvulopathy • Caution with patient use of hazardous machinery because of the potential for cognitive impairment with disturbances in attention or memory • Caution among patients with psychiatric disorders, including euphoria and dissociation. • Caution among patients with psychiatric disorders and predisposed to depression, who should be monitored for depression or suicidal thoughts, with discontinuation of lorcaserin if symptoms develop • Weight-loss lorcaserin may produce hypoglycemia in patients treated for T2DM • Caution in patients with history of priapism or predisposition to priapism • Pregnancy or nursing mothers
Potential drug interactions	<ul style="list-style-type: none"> • The safety of lorcaserin coadministration with other serotonergic or antidopaminergic agents is not yet established, which includes selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, triptans, bupropion, dextromethorphan, St. John's Wort.
Metabolism	<ul style="list-style-type: none"> • Lorcaserin is metabolized in the liver with metabolites excreted in the urine.
Administration	<ul style="list-style-type: none"> • One 10 mg tablet twice daily • Discontinue if 5% weight loss is not achieved by week 12
Pregnancy	<ul style="list-style-type: none"> • Lorcaserin is pregnancy category X at least in part on the basis that weight loss offers no potential benefit to a pregnant woman and may result in fetal harm.

Phentermine/topiramate controlled-release

Phentermine/topiramate controlled-release (PHEN/TPM CR) (Tables 13, 16 and 17) was approved as a weight management agent in 2012. The three sentinel phase 3 PHEN/TPM CR trials included the EQUIP trial,²⁶⁸ the EQUATE trial,²⁵⁶ and the CONQUER trial.²⁶⁹ The PHEN/TPM development program and the effects of PHEN/TPM on adiposopathy were previously reviewed.^{255,256} As an illustrative example, the placebo-controlled EQUIP trial evaluated PHEN/TPM 3.75/23 mg or PHEN/TPM 15/92 mg per day in a year-long trial of 1267 obese subjects (BMI ≥ 35 kg/m², with mean baseline BMI = 42 kg/m²).²⁶⁸ The most frequent adverse experiences were paresthesia, dry mouth, constipation, dysgeusia, and insomnia. In the intent-to-treat analysis after 1 year, the percent weight loss among placebo, PHEN/TPM CR 3.75/23 mg, and PHEN/TPM CR 15/92 mg was 1.6%, 5.1%, and 10.9%, respectively (all $P < .0001$). The range of baseline lipid levels in these three groups included total cholesterol 193 to 196 mg/dL, LDL-C 120 to 123 mg/dL, HDL-C 49 to

50 mg/dL, and TGs 114 to 118 mg/dL. The respective percent change in lipid parameters after 1 year in the placebo, PHEN/TPM CR 3.75/23 mg, and PHEN/TPM CR 15/92 mg groups were a 3.5%, 5.4%, and 6.0% reduction in total cholesterol; 5.5%, 7.7%, and 8.4% reduction in LDL-C; 0%, 0.5%, and 3.5% increase in HDL-C; and +9.1%, +5.2%, and -5.2 percent change in TG levels, respectively. All the lipid changes regarding the PHEN/TPM full dose of 15/92 were statistically significant versus placebo. In a patient population without substantial dyslipidemia, the placebo-corrected 3.5 to ~9% weight loss found with PHEN/TPM CR 3.75/23 mg, and PHEN/TPM CR 15/92 mg may produce placebo-corrected mild reductions in total cholesterol and LDL-C, with the greatest reduction in TG levels (as much as 14% placebo-corrected) being with the full PHEN/TPM dose of 15/92 mg per day, which was the dose that produced the greatest weight loss. In a subsequent analysis of a subgroup of dyslipidemic patients, regardless of treatment assignment, those who lost $\geq 5\%$ of their baseline weight experienced significantly greater reductions in TG levels (-14.5% to -39.8%), and

Table 16 Topiramate summary²⁵⁵

Class of agent	<ul style="list-style-type: none"> • Antiepileptic drug • Migraine prophylaxis drug • No DEA scheduled listing (not a controlled substance)
Mechanisms of action	<ul style="list-style-type: none"> • Topiramate is a sulfamate-substituted monosaccharide neurostabilizer via modification of excitatory voltage-activated sodium and calcium channels, antagonism of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid kainite receptors, and enhancement of gamma-aminobutyric acid receptor-mediated inhibitory currents
Potential adverse effects	<ul style="list-style-type: none"> • Difficulty with concentration, memory, cognition, psychomotor slowing, mood changes with nervousness, anxiety and depression • Antiepileptic drugs may increase the risk of suicidal ideations • Topiramate is a carbonic anhydrase inhibitor, which may contribute to: <ul style="list-style-type: none"> ○ Metabolic acidosis ○ Increased risk of kidney stones ○ Oligohydrosis potentially contributing to hyperthermia, especially in children ○ Paresthesias ○ Anorexia ○ Taste perversion ○ Dizziness ○ Fatigue ○ Somnolence • As with some other sulfa-based drugs, topiramate may cause secondary angle closure glaucoma (mostly dose-related) clinically manifested by acute myopia, sudden onset of blurring of vision, redness of the sclera, photophobia and discomfort of the eyes • Potential laboratory abnormalities include decreased bicarbonate, decreased phosphorous, increased alkaline phosphatase, decreased potassium, and hyperammonemia with encephalopathy
Contraindications and cautionary use	<ul style="list-style-type: none"> • Acute myopia and secondary angle closure glaucoma • Dose should be reduced in patients with renal impairment • Topiramate blood concentrations may increase in patients with impaired hepatic function • Pregnancy or nursing mothers
Potential drug interactions	<ul style="list-style-type: none"> • Concomitant treatment of topiramate with valproic acid may cause hypothermia and accentuate hyperammonemia and encephalopathy
Metabolism	<ul style="list-style-type: none"> • Topiramate is mainly excreted by the kidney
Administration	<ul style="list-style-type: none"> • Topiramate is typically prescribed 50 mg twice a day (total of 100 mg/day) for migraine prophylaxis, and up to 200 mg twice a day (total of 400 mg/day) for treatment of seizures
Pregnancy	<ul style="list-style-type: none"> • Topiramate is pregnancy category D

in non-HDL cholesterol (−9.4% to −14.8%) than those losing <5% of their weight ($P < .05$).²⁷⁰

Naltrexone SR/bupropion SR

The sentinel phase 3 clinical trials for the investigational naltrexone sustained-release (SR) 32 mg/bupropion SR 360 mg/day (NB32) and naltrexone SR 16 mg/bupropion SR 360 mg/day (NB16) (Tables 18 and 19) include the Contrave Obesity Research (COR) programs. COR-I (NB-301) was a 58-week study assessing the safety and efficacy of naltrexone/bupropion in 1742 healthy, obese patients without T2DM. COR-II (NB-303) was a 56-week study designed to assess the safety and efficacy of naltrexone/bupropion in 1496 healthy, obese patients without T2DM. COR-Diabetes (NB-304) was a 56-week study designed to assess the safety and

efficacy of naltrexone/bupropion in 505 obese subjects who also have been diagnosed with T2DM. COR-BMOD (NB-302) was a 56-week study designed to evaluate the safety and efficacy of naltrexone/bupropion alone or when combined with intense diet, exercise, and behavior modification in approximately 800 patients. Finally, in addition to these phase 3 trials, “The Light Study” is an ongoing cardiovascular outcome study of naltrexone SR/bupropion SR in overweight and obese subjects with CVD risk factors.

As an illustrative example in the COR-1 study,²⁷¹ both NB32 and NB16 significantly reduced body weight versus placebo (−6.1% and −5.0% vs. −1.3%, respectively, $P < .0001$ for each comparison). The most frequent adverse experiences reported in NB administered subjects included nausea, headache, constipation, dizziness, vomiting, and dry mouth. Subjects administered NB also experienced a

transient ~ 1.5 mmHg increase in mean systolic and diastolic blood pressure, followed by a reduction of around 1 mm Hg below baseline. Compared with placebo, NB was not associated with increased depression or suicide. The baseline lipid parameters included LDL-C 120 mg/dL (~ 3.1 mmol/L), TGs 115 mg/dL (~ 1.3 mmol/L), and HDL-C levels 52 mg/dL (~ 1.35 mmol/L). NB32 significantly reduced TG levels and raised HDL-C levels versus placebo. Specifically, after 56 weeks, the percent change of NB32 versus placebo on LDL-C, TGs, and HDL-C were -2.0% versus -0.5% , -12.7% versus -3.1% , and 8% versus 0.8% , respectively. In patients without substantial dyslipidemia, NB32 modestly reduced TG and LDL-C levels and increased HDL-C levels versus placebo. The reduction in TG levels based upon higher versus lower baseline TG levels (eg, tertile analysis) was not reported.

The impact of bariatric surgery and weight loss on lipids

To comprehend the various lipid alterations that occur with Roux-en-Y gastric bypass (RNYGB), laparoscopic adjustable gastric banding (LAGB), and laparoscopic sleeve gastrectomy (LSG), it is imperative to know the basic anatomic and physiologic changes that occur with each of these procedures such as which one is solely restrictive versus restrictive and malabsorptive, as well as which procedures are permanent versus reversible.²⁷² The change in gut hormone concentrations caused by bariatric surgery also contributes to the varying effects on lipid profile.^{186,273}

Although there appears to be agreement on the beneficial effects of RNYGB, LAGB, and LSG on total cholesterol, LDL-C, TGs, and HDL-C, there are nuances in the degree to which each lipid fraction is altered depending on which bariatric procedure is chosen.^{186,274} A paucity of data exist on whether the longevity of these beneficial lipid alterations is solely related to the degree of weight loss or if varying hormonal changes caused by these procedures contribute to the subtleties in lipid alteration over time. It is yet to be determined whether the lipid alterations produced by bariatric procedures will reduce long-term CVD mortality.²⁷⁵

Surgical treatments for adiposopathy

RNYGB is the oldest procedure that is known to cause weight loss and metabolic changes by restricting gastric size and rerouting the gut. Gastric bypass involves creation of a small (20–30 mL) stomach pouch located at the distal end of the esophagus, which is sometimes surgically divided from the rest of the stomach. The next step is the division of the jejunal portion of the small intestine into a proximal limb (which maintains its attachment to the duodenum), and a distal limb which is then connected to the newly created stomach pouch creating a gastrojejunostomy. The part of the jejunum that is brought up and joined to the upper stomach pouch is called the “Roux Limb,” named after a Swiss surgeon. The result is that ingested

food goes from the esophagus, into the small stomach pouch, and then directly into the jejunum, thus “bypassing” most of the stomach and the duodenum. Regarding the location of the jejunal divide, the further distal the jejunum is severed, the less small intestine remains in the roux limb, and the less opportunity for absorbing nutrients. Finally, the last step in this procedure is that the residual proximal jejunal limb (attached to the duodenum and stomach) must have somewhere to drain its gastric, pancreatic, and biliary fluids. Therefore, this small intestinal limb section undergoes anastomosis somewhere down the small intestine Roux limb, resulting in a jejunojejunostomy, which completes the “Y” configuration (Fig. 21). This procedure is now most commonly performed laparoscopically, which has reduced mortality and morbidity significantly.

A more recent surgical intervention used since the 1980s is LAGB. In this procedure, an inflatable silicone ring is laparoscopically placed around a proximal portion of the stomach. The band diameter can be adjusted via a subcutaneous port, resulting in a greater or lesser limitation of food passage from the esophagus and proximal stomach, into the rest of the stomach beyond the band. No division or anastomosis of the intestine is involved, making this a purely restrictive procedure as opposed to the RNYGB, which has both a restrictive and malabsorptive effect.

The most recent procedure is LSG, which came into practice in 1993. LSG produces weight loss through gastric restriction-like banding but does not introduce a foreign body such as in LAGB. The stomach is restricted by stapling and dividing it vertically and removing more than 85% of it (this can be done laparoscopically or open). In contrast to LAGB, this procedure is not reversible. The stomach that remains is thin and tubular and measures from 30 to 150 mL.²⁷⁶ The innervation to the stomach and the pylorus are spared preserving gastric functionality yet reducing the volume. There is no rerouting of the gut with this procedure, which limits complications such as vitamin deficiencies and malabsorption.

In addition, the portion of the stomach that is removed in LSG is responsible for secreting the orexigenic hormone, ghrelin. By removing this portion of the stomach rather than leaving it in-place, the level of ghrelin is reduced, actually causing a reduction in appetite and enhancing the effect of the producer.²⁷⁷

Effects of bariatric surgery on weight loss

RNYGB has been shown to be the superior surgical method for inducing weight loss in randomized, prospective trials, which is often reported as excess weight loss, weight loss divided by (initial body weight - ideal body weight).²⁷⁸ One long term study reported a series with 58%, 55%, and 49% excess weight loss at 5, 10, and 14 years from surgery, respectively.²⁷⁹ A more recent study reported a 62% excess weight loss at 10 years.²⁸⁰ Long-term maintenance of weight loss after RNYGB is excellent and modifications to the length of the Roux limb may achieve better

Table 17 Phentermine HCl/topiramate controlled-release combination agent (PHEN/TPM CR) Summary*,^{255,256,282}

Class of agent	<ul style="list-style-type: none"> ● PHEN/TPM CR is a weight management agent ● Drug Enforcement Agency Scheduled IV drug <p>Phentermine</p> <ul style="list-style-type: none"> ● Phentermine is a sympathomimetic amine (noradrenergic, with minimal dopaminergic activity) related to amphetamine, but with minimal abuse potential ● Increased satiety with no appreciable effect on energy expenditure
Mechanism/s of action	<p>Topiramate</p> <ul style="list-style-type: none"> ● Topiramate is a neurostabilizer via modification of excitatory voltage-activated sodium and calcium channels, antagonism of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid kainite receptors, and enhancement of gamma-aminobutyric acid receptor-mediated inhibitory currents ● Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid kainite receptor antagonism may reduce compulsive or addictive food cravings, as supported by an improvement in binge eating disorder, and reducing other addictive behaviors ● Activation of gamma-aminobutyric acid receptors with topiramate may decrease nighttime and deprivation-induced feeding ● Animal studies suggest topiramate may increase neuropeptide Y in the hypothalamus (which may promote positive caloric balance); however, topiramate may increase hypothalamic corticotropin-releasing hormone, which is catabolic. ● Topiramate may increase hypothalamic galanin, which may influence body weight regulation ● Although topiramate-induced weight reduction may decrease leptin, such a decrease in leptin with topiramate may be blunted, which may favor persistence of weight loss ● Topiramate may not reduce objective measures of appetite during weight loss, which may favor persistence of weight loss ● Topiramate may inhibit adipocyte mitochondrial carbonic anhydrase isozyme V, inhibiting carbonic anhydrase-mediated lipogenesis ● Topiramate may decrease LPL activity in white adipose tissue, which would limit free fatty acid substrate for lipogenesis ● Topiramate may increase LPL activity in brown adipose tissue, which may indicate increased thermogenesis, and increase LPL activity in skeletal muscle, further supporting the potential for substrate oxidation ● Topiramate may increase adiponectin levels, which favorably affects many peripheral physiologic processes relevant to metabolic disease ● Topiramate may alter taste (possibly via carbonic anhydrase inhibition), and thereby reduce caloric intake ● Topiramate is a carbonic anhydrase inhibitor, which may have anorexigenic effects. ● Although studies in animals suggest topiramate may decrease energy storage and usage efficiency, increase energy expenditure, and increase thermogenesis, human studies do not support weight loss with topiramate as being due to an increase in energy expenditure
Potential adverse effects	<ul style="list-style-type: none"> ● Adverse reactions occurring greater than or equal to 5% include: <ul style="list-style-type: none"> ○ Paresthesia ○ Dizziness ○ Dysgeusia (taste distortion/perversion) ○ Insomnia ○ Constipation ○ Dry mouth ● Laboratory abnormalities include: <ul style="list-style-type: none"> ○ Metabolic acidosis ○ Elevated creatinine ○ Lowering of glucose levels

Contraindications and cautionary use	<ul style="list-style-type: none"> ● PHEN/TPM CR is contraindicated: <ul style="list-style-type: none"> ○ During pregnancy ○ Glaucoma ○ Hyperthyroidism ○ During or within 14 days of taking monoamine oxidase inhibitors ● Women of reproductive potential should have negative pregnancy test before treatment and monthly thereafter, and use effective contraception while on PHEN/TPM CR ● PHEN/TPM CR should be discontinued in patients with: <ul style="list-style-type: none"> ○ Unacceptable increases in adrenergic responses, such as increase in heart rate especially those with cardiac and/or cerebrovascular disease ○ Suicidal behavior and ideation ○ Acute myopia and secondary angle closure glaucoma ○ Unacceptable mood and sleep disorders ○ Cognitive impairment ○ Pregnancy or nursing
Potential drug interactions	<ul style="list-style-type: none"> ● PHEN/TPM CR may alter the exposure to oral contraceptives, causing irregular menstrual bleeding, but not an increased risk of pregnancy. Oral contraceptives should not be discontinued if spotting occurs. ● PHEN/TPM CR may potentiate central nervous system depressants such as alcohol; thus, patients should avoid concomitant alcohol ● PHEN/TPM CR may potentiate hypokalemia of non-potassium sparing diuretics
Metabolism	<ul style="list-style-type: none"> ● Phentermine is metabolized by the liver, with most excreted by the kidney. ● Topiramate is excreted mainly by the kidney
Administration	<ul style="list-style-type: none"> ● PHEN/TPM CR should be taken once daily in morning. ● Recommended titration: Start with 3.75-mg/23-mg (phentermine 3.75 mg/topiramate 23 mg extended-release) daily for 14 days, then increase to 7.5 mg/46 mg daily. ● Dose should be discontinued or escalated if 3% weight loss is not achieved after 12 weeks on 7.5 mg/46 mg dose ● PHEN/TPM CR should be discontinued if 5% weight loss is not achieved after 12 weeks on maximum daily dose of 15 mg/92 mg ● If maximum dose is to be discontinued, then it should be done gradually to prevent possible seizure
Pregnancy	PHEN/TPM CR is pregnancy category X.

LPL, lipoprotein lipase.

*The components of PHEN/TPM CR (phentermine and topiramate controlled release) in this combination agent are at lower doses than typically prescribed when phentermine and topiramate are used for their individual indications (see Tables). Most adverse experiences to phentermine and topiramate are dose-related. The description of adverse experiences (AEs) of PHEN/TPM CR in this table are not all inclusive, but rather a summary of the more clinically applicable AEs. A more comprehensive description of AEs can be derived from the review of the individual components (as per the Tables of the individual tables above), as well as via the Prescribing Information.²⁸²

Table 18 Naltrexone summary²⁸⁹

Class of agent	<ul style="list-style-type: none"> ● Opioid antagonist used for treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids.
Mechanism/s of action	<ul style="list-style-type: none"> ● Naltrexone markedly, but reversibly, attenuates or completely blocks the subjective effects of intravenously administered opioids, reducing the physical dependence to morphine, heroin and other opioids, as well as alcohol
Potential adverse effects	<ul style="list-style-type: none"> ● Nausea ● Hepatocellular injury when given in excessive doses. ● In alcoholic patients, naltrexone may cause withdrawal symptoms, such as tearfulness, mild nausea, abdominal cramps, restlessness, bone or joint pain, myalgia, and nasal symptoms ● Other symptoms in alcoholic patients include headache, dizziness, nervousness, fatigue, insomnia, vomiting, anxiety, somnolence, depression, suicidal ideations, and suicide attempts.
Contraindications and cautionary use	<ul style="list-style-type: none"> ● Naltrexone is contraindicated in patients: <ul style="list-style-type: none"> ○ Receiving opioid analgesics. ○ Currently dependent on opioids ○ Currently maintained on opiate agonists (eg, methadone or levo-alpha-acetyl-methadol). ○ In acute opioid withdrawal ○ Who have failed the naloxone challenge test ○ With positive urine screen for opioids. ○ Acute hepatitis or liver failure
Potential drug interactions	<ul style="list-style-type: none"> ● Many potential drug interactions have yet to be determined ● The concomitant use of two potentially hepatotoxic medications is not ordinarily recommended unless the probable benefits outweigh the known risks. ● Lethargy and somnolence have been reported following doses of naltrexone hydrochloride and thioridazine ● Patients taking naltrexone may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics ● In an emergency situation when opioid analgesia must be administered to a patient receiving naltrexone, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged
Metabolism	<ul style="list-style-type: none"> ● Naltrexone is a highly extracted drug (>98% metabolized), including extra-hepatic metabolism. The urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6-β-naltrexol accounts for 43% of an oral dose. The pharmacokinetic profile of Naltrexone suggests that naltrexone and its metabolites may undergo enterohepatic recycling. Adequate studies of Naltrexone in patients with severe hepatic or renal impairment have not been conducted.

Administration

- For treatment of alcoholism, a dose of 50 mg once daily is recommended for most patients for up to 12 weeks.
- For treatment of opioid dependence, the starting naltrexone dose is 25 mg per day. If no withdrawal signs occur, the dose is increased to 50 mg a day afterwards.
- Treatment of opioid dependence should not be attempted until the patient has remained opioid-free (by objective urine testing) for at least 7–10 days, and is not manifesting withdrawal signs or reporting withdrawal symptoms.
- If any question exists of occult opioid dependence, a naloxone challenge test is performed. If signs of opioid withdrawal are still observed after naloxone challenge, treatment with naltrexone hydrochloride should not be attempted. The naloxone challenge can be repeated in 24 hours.
- Naloxone challenge test:
 - Should not be performed in patients exhibiting clinical signs or symptoms of opioid withdrawal, or whose urine contains opioids.
 - Intravenous:
 - Inject 0.2 mg of naloxone
 - Observe for 30 seconds for signs or symptoms of withdrawal.
 - If no evidence of withdrawal, inject 0.6 mg of naloxone
 - Observe for an additional 20 minutes
 - Subcutaneous: Administer 0.8 mg naloxone
 - Observe for 20 minutes for signs or symptoms of withdrawal
 - Signs and symptoms of opioid withdrawal may include nausea, vomiting, dysphoria, yawning, sweating, tearing, rhinorrhea, stuffy nose, craving for opioids, poor appetite, abdominal cramps, sense of fear, skin erythema, disrupted sleep patterns, fidgeting, uneasiness, poor ability to focus, mental lapses, muscle aches or cramps, pupillary dilation, piloerection, fever, changes in blood pressure, pulse or temperature, anxiety, depression, irritability, backache, bone or joint pains, tremors, sensations of skin crawling, or fasciculations.
 - If signs or symptoms of withdrawal appear, the test is positive and no additional naloxone should be administered
 - If the naltrexone challenge test is positive, naltrexone therapy should not be started. May repeat in 24 hours. If the test is negative, naltrexone hydrochloride therapy may be started if no other contraindications are present. If there is any doubt about the result of the test, hold naltrexone hydrochloride and repeat the challenge in 24 hours.

Pregnancy

Naltrexone is pregnancy category C

Table 19 Bupropion summary²⁷³

Class of agent	<ul style="list-style-type: none"> ● Bupropion is indicated for the treatment of major depressive disorder ● Some bupropion formulations are approved for smoking cessation ● Some bupropion formulations are approved for treating seasonal affective disorder
Mechanism/s of action	<ul style="list-style-type: none"> ● Bupropion an antidepressant of the aminoketone class chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. ● Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine ● Does not inhibit monoamine oxidase or the re-uptake of serotonin.
Potential adverse effects	<ul style="list-style-type: none"> ● Changes in mood: <ul style="list-style-type: none"> ○ Depression ○ Mania ○ Psychosis ○ Hallucinations ○ Paranoia ○ Delusions ○ Homicidal ideation ○ Hostility ○ Agitation ○ Aggression ○ Anxiety ○ Excitement ○ Panic ○ Suicidal ideation, suicide attempt, and completed suicide. ● Rash ● Pruritis ● Edema ● Nausea ● Drowsiness ● Insomnia ● Migraine headache ● Dizziness ● Seizures ● Anorexia ● Dry mouth ● Constipation ● Diaphoresis ● Palpitations ● Chest pain ● Tinnitus ● Tremor ● Abdominal pain ● Pharyngitis ● Myalgia ● Urinary frequency
Contraindications and cautionary use	<ul style="list-style-type: none"> ● Seizure disorder. ● Current or previous diagnosis of bulimia or anorexia nervosa ● Abrupt discontinuation of alcohol or sedatives (including benzodiazepines) ● Concurrent administration monoamine oxidase inhibitor is contraindicated.
Potential drug interactions	<ul style="list-style-type: none"> ● Because bupropion is primarily metabolized by the CYP2B6 isoenzyme, potential exists for a drug interactions with substrates of or inhibitors/inducers of the CYP2B6 isoenzyme (eg, orphenadrine, thiotepa, cyclophosphamide, ticlopidine, and clopidogrel). ● Although Bupropion is not metabolized by this the CYP2D6 isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme which metabolizes drugs such as most antidepressants (selective serotonin reuptake inhibitors, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics ● Paroxetine, sertraline, norfluoxetine, fluvoxamine, nelfinavir, and efavirenz may inhibit the hydroxylation of bupropion

(continued on next page)

Table 19 (continued)

Metabolism	<ul style="list-style-type: none"> • Bupropion doses may need to be increased (but not above the maximal approved dose) in patients receiving ritonavir or ritonavir plus lopinavir. • Some anti-seizure drugs may induce the metabolism of bupropion (eg, carbamazepine, phenobarbital, phenytoin) • Animal studies suggest the acute toxicity of bupropion is enhanced by monoamine oxidase inhibitors • May increase adverse experiences with levodopa and amantadine • Bupropion is primarily metabolized by the CYP2B6 isoenzyme, and is an inhibitor of the CYP2D6 isoenzyme • Bupropion is extensively metabolized, and metabolites are mainly eliminated in the urine (87%) and feces (10%).
Administration	<ul style="list-style-type: none"> • Nonsustained-release bupropion is taken three to four times per day • Sustained-release bupropion is taken twice a day • Doses vary depending upon indicated and intended use and clinical response
Pregnancy	<ul style="list-style-type: none"> • Bupropion is pregnancy category C

weight loss in extreme obesity (BMI ≥ 50 kg/m²) patients, although the potential for nutrition deficiencies increases as well.²⁸⁰

Weight loss results after LAGB have been more variable with some studies reporting 35% loss of excess body weight and some reporting as high as 65% loss of excess weight. Some of these discrepancies may be attributable to differing management of band adjustment amongst surgeons. A study by Westling et al, reported a 56% loss of excess weight at 2 years in 90 patients, but with a disappointing 35% conversion to RNYGB. One study reported 50% of patients required LAGB removal within 42 months after surgery and only 11% of patients achieved a BMI <35 kg/m² and/or at least 50% reduction in excess weight without complications.²⁸¹

Reduction in excess weight for laparoscopic LSG appears to be intermediate between that of RNYGB and LAGB. Fischer et al published a literature review looking at 123 papers that reported weight loss data from >12,000 sleeve gastrectomies performed. At 12 months, the mean excess weight loss for LSG was significantly lower when compared to patients who underwent gastric bypass (SG 56.1%, gastric bypass 68.3%; $P < .01$).²⁸² In a study comparing LSG to LAGB, both procedures produced a significant decrease in total weight and BMI but excess weight loss was superior in the LSG versus LAGB group at 2 years.²⁸³

Effects of bariatric surgery on lipid profiles

The effects of bariatric surgery on lipid levels can be illustrated by the results of the Swedish Obese Subjects Study (SOS), in which investigators evaluated 2010 subjects who underwent gastric surgery (eg, gastric bypass, banding, and vertical banded gastroplasty) compared with 2037 matched, obese control subjects. Compared with usual care, bariatric surgery was associated with long-term reduction in overall mortality.²⁸⁴

In a 10-year follow-up of the SOS, body weight increased by 1.6% in the control group and decreased 16.1% in the

combined surgery group (Fig. 22). This was associated with more favorable effects upon T2DM and hypertension among the surgery group versus the control group. With regard to changes in lipid levels at 10 years, bariatric surgery produced favorable effects on TG levels (2.2% vs -16.3%; $P < .001$, control vs surgery) and HDL-C levels (10.8% vs 24.0%, $P < .001$, control vs surgery). Furthermore, the incidence rates of hypertriglyceridemia were markedly lower in the surgically treated group than in the control group after 2 and 10 years, whereas the incidence of low HDL-C was significantly lower in the surgery group after 2 years but not after 10 years (Fig. 23). The incidence of hypercholesterolemia did not differ between the groups over the 2- and 10-year periods (Fig. 23).

Similar to its effect on weight loss, the lipid-lowering effect appears to be greatest for RNYGB.²⁸⁵ This cannot be attributed only to the greater excess weight loss but also to the endocrine changes that occur after RNYGB such as increased glucagon like peptide, adrenocorticotrophic hormone, and peptide YY, as well as decreased insulin, insulin like growth factor-1, leptin, and ghrelin.²⁸⁶ These hormonal changes have been noted before weight loss and likely contribute to the sustained lipid lowering effects that have been observed even in the face of weight regain many years after gastric bypass.^{286,287} A 2006 retrospective study by Nguyen et al looking at 95 severely obese patients who underwent laparoscopic RNYGB showed substantially improved lipid profiles as early as 3 months postoperatively and these alterations were sustained at 1 year.²⁸⁸ Mean percentage of excess body weight loss at 12 months postoperatively was 66%. One year after gastric bypass, mean total cholesterol levels decreased by 16%; TG levels decreased by 63%; LDL-C levels decreased by 31%; VLDL-C decreased by 74%; total cholesterol/HDL-C risk ratio decreased by 60%, and HDL-C levels increased by 39%. Also, within 1 year, 23 of 28 (82%) patients requiring lipid-lowering medications preoperatively were able to discontinue their medications. A more recent study looked at lipid and glucose alterations at 6, 12, and 18 months. Total

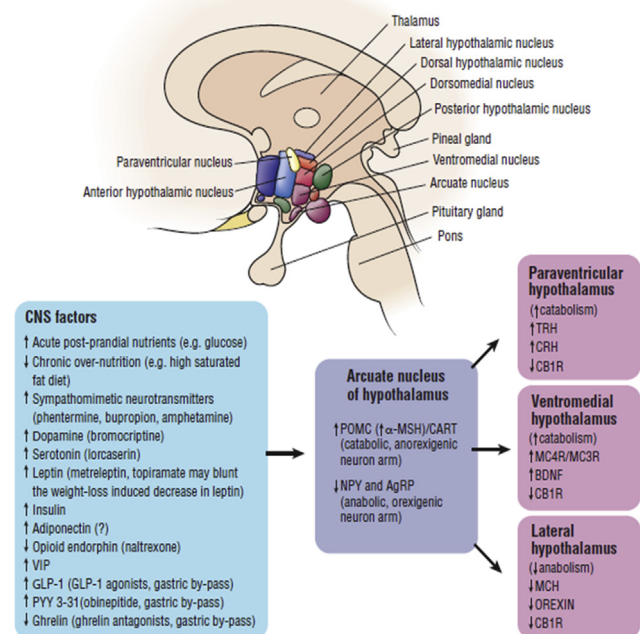


Figure 20 Regarding central nervous system (CNS) factors, up arrows mean that an increase in the listed CNS factor increases arcuate nucleus Proopiomelanocortin (POMC)/cocaine and amphetamine regulated transcript (CART) activity and/or decreases neuropeptide Y (NPY) and/or agouti-related peptide (AgRP) activity, and thus increases catabolism and/or decreases anabolism. A down arrow means that a decrease in the CNS factor also increases catabolism and/or decreases anabolism via the arcuate nucleus. Catabolism, predominantly through anorexigenic effects (promoting lipolysis if negative caloric balance is achieved), may occur if a stimulus increases the production of POMC, which is cleaved to form melanocortins [such as melanocyte stimulating hormone (MSH)] and CART. Similarly, and often simultaneously, catabolism is further promoted through decreased orexigenic expression of NPY and AgRP. Reproduced with permission.¹³ BDNF, brain-derived neurotrophic factor; CB1-R, cannabinoid 1 receptor; CRH, corticotropin-releasing hormone; GLP-1, glucagon-like peptide-1; MC3 R, melanocortin 3 receptor; MC4 R, melanocortin 4 receptor; MCH, melanin-concentrating hormone; MSH, melanocyte-stimulating hormone; PYY 3–31, peptide YY; TRH, thyroid-releasing hormone; VIP, vasoactive intestinal peptide.

cholesterol, LDL-C, TGs, and HOMA-IR were significantly reduced after laparoscopic RNYGB, whereas HDL-C showed a significant increase. This study showed a significant association between lipid subfractions and excess weight lost.²⁸⁹

Similar results have been seen after gastric bypass in the pediatric populations as well with the above lipid changes present at 2 year follow up.²⁹⁰ Results from a large observational study performed on 949 patients who underwent RNYGB from 2005 to 2010 are in concordance with the retrospective analyses mentioned above. Subjects showed favorable metabolic changes after a mean of 388 days. LDL-C decreased from a mean of 108 to 87 mg/dL, HDL-C increased a mean of 10 mg/dL in men and women,

and of the 15% of patients who had TGs >200 mg/dL before surgery, only 1.1% had hypertriglyceridemia in follow-up. In addition, of the 33% of patients who had T2DM preoperatively, 66% of those patients achieved a hemoglobin A_{1c} (HbA_{1c}) of <6.5% after surgery. The mean CRP decreased from 5.0 to 1.6 mg/dL.²⁹¹

In addition to monitoring the major lipid fractions, other lipid and related parameters are affected as after RNYGB, which may have implications regarding long-term CVD mortality. In a 2010 study, Asztalos et al looked at plasma lipoproteins and glucose homeostasis before and after RNYGB surgery in 19 morbidly obese women.²⁹² Standard lipid fractions, remnant-lipoprotein cholesterol (RLP-C), apolipoproteins, lecithin cholesterol acyltransferase (LCAT), CETP mass and activity, plasma glucose, and insulin levels were measured before and at 1, 3, 6, and 12 months after RNYGB surgery. Baseline concentrations of TG, RLP-C, glucose, and insulin were significantly greater in obese than in normal-weight, age-matched women, whereas HDL-C, apo A-I, apo A-II, and alpha-1 HDL and alpha-2 HDL subfraction levels were significantly lower. Over 1 year, significant decreases in BMI, glucose, insulin, TG, RLP-C, and prebeta-1 HDL levels were observed with significant increases of HDL-C and alpha-1 HDL levels. Changes in fat mass directly correlated with LDL-C and LCAT mass but not with CETP mass. Changes of fasting plasma glucose concentrations were inversely correlated with those of CETP mass and alpha-1 HDL level. Changes of fasting plasma insulin concentrations were positively correlated with those of LCAT mass and inversely with changes of alpha-1 HDL and alpha-2 HDL concentrations. These results demonstrate beneficial changes in HDL-C remodeling after substantial weight loss induced by RNYGB surgery and that these changes are associated with improvement of glucose and lipid homeostasis in these patients.

Tantamount to improvements in major lipid fractions and plasma lipoproteins in reducing CVD mortality is the change in inflammatory markers and adipokines that occurs after RNYGB. Twelve months after surgery, there was a significant increase in plasma levels of adiponectin and HDL-C and a significant decrease in levels of IL-6, CRP, total cholesterol, TGs, LDL-C, glucose, insulin, and HOMA-IR. At 12 months, correlations were seen between IL-6 levels and the following: BMI, insulin and HOMA-IR. Also, CRP levels correlated with BMI, TGs, insulin and HOMA-IR.²⁹³ This study supports the hypothesis that adiposity is a low-grade inflammatory state. In patients with morbid obesity, significant weight loss is followed by a significant improvement in the inflammatory state, insulin sensitivity and lipid profile. An area that requires further study is whether these lipid, glucose, and inflammatory markers continue to show positive changes in the long-term and whether this correlates to reduced CV risk. Donadelli et al²⁷⁵ looked at lipid alterations at 2 years post-RNYGB and calculated Framingham Risk based on the metabolic parameters present at that time. Forty-two patients were included in the study. A significant reduction of 10-year CVD

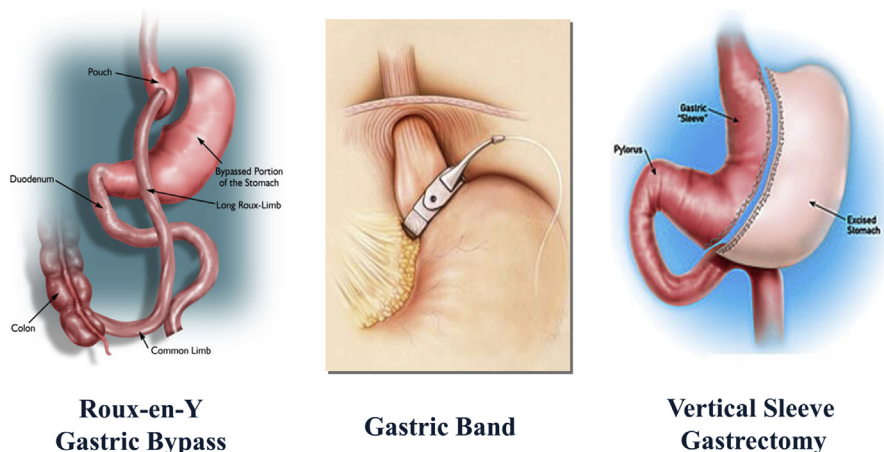


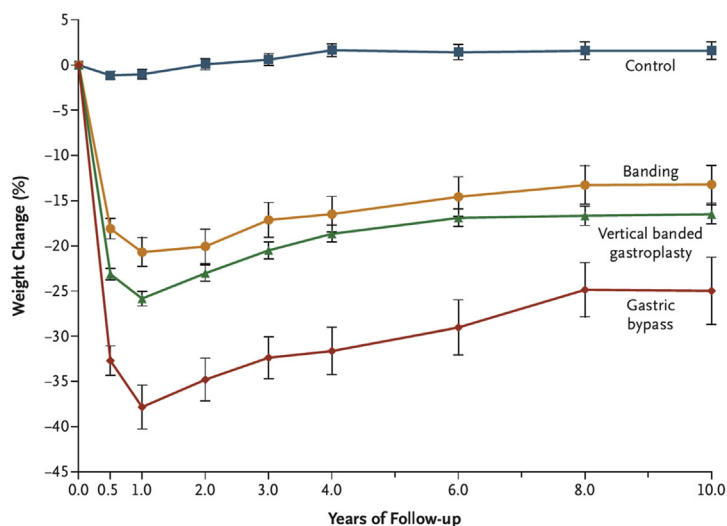
Figure 21 RNYGB, LAGB, and LSG. Reproduced with permission from <http://www.ncsurgical.net/>.

risk was mainly associated with weight reduction and improvement of comorbidities associated with adiposity. The benefits were greater among patients who already presented known risk factors such as T2DM and hypertension.

Although most of the data on lipid alterations are on gastric bypass surgery, there is increasing evidence that favorable parameters are achieved with LAGB and LSG as well. Being that many patients may opt for these 2 less severe procedures due to lower short-term morbidity, it is necessary to look at comparative effects. In a trial of RNYGB versus LAGB, RNYGB patients had lost 77% of their excess weight and had significant improvements in total cholesterol, LDL-C, HDL-C, TGs, TG/HDL ratio, homocysteine-C, CRP, fasting insulin, and HbA1C whereas LAGB patients lost 47.6% of their excess weight and had

significant improvements in TGs, TG/HDL ratio, HmC, CRP, and HbA1c.²⁹⁴ Having RNYGB instead of LAGB was predictive of significantly greater improvements in total cholesterol at 12 months postoperatively.

Because laparoscopic LSG is the most recent bariatric procedure to be introduced as an option for weight-loss surgery, only few studies have looked at long-term metabolic consequences, and data are conflicting regarding this procedure. In a recent small surgical study examining LSG versus RNYGB, Iannelli et al²⁸⁵ found that metabolic syndrome improved in all five patients undergoing RNYGB and in four of six patients undergoing LSG. At 1 year after surgery, patients in the RNYGB group had a significantly lower BMI and percent of excess BMI lost and had significantly lower plasma levels of



No. of Subjects	0.0	0.5	1.0	2.0	3.0	4.0	6.0	8.0	10.0
Control	627	585	594	587	577	563	542	535	627
Banding	156	150	154	153	149	150	147	144	156
Vertical banded gastroplasty	451	438	438	438	429	417	412	401	451
Gastric bypass	34	34	34	34	33	32	32	29	34

Figure 22 Weight changes (% change from study inclusion) among participants in the SOS study receiving different types of bariatric surgical procedures during a 10-year period. All data are for subjects who completed 10 years of the study. The average weight change in the entire group of surgically treated subjects was -16.1%. The error bars represent 95 percent confidence intervals. Reproduced with permission.³⁸⁴

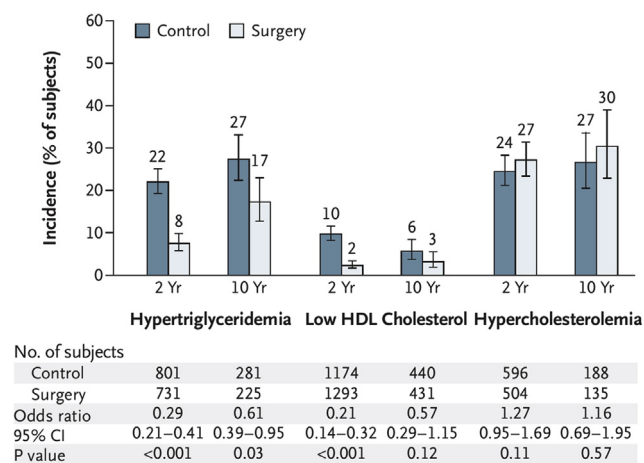


Figure 23 Incidence of lipid disturbances among subjects in the SOS study during 2- and 10-year periods. Data are for subjects who completed 2 years and 10 years of the study; all surgical groups compared with all controls. The bars and corresponding values above indicate unadjusted incidence rates; error bars represent the corresponding 95 percent confidence intervals (95% CI). The odds ratios, 95% CIs for the odds ratios, and P values have been adjusted for gender, age, and BMI at the time of inclusion in the intervention study. Hypertriglyceridemia = ≥ 150 mg/dL; low HDL-C = ≤ 39 mg/dL; hypercholesterolemia = ≥ 201 mg/dL. Reproduced with permission.³⁸⁴

CRP, total cholesterol, and LDL-C. Remission of metabolic syndrome was significantly less common after LSG at 1 year than RNYGB. This small study demonstrated significantly lower BMIs, improved lipid profiles, decreased systemic low-grade inflammation and less metabolic syndrome in RNYGB patients than those with LSG at 1-year follow-up.

A more recent prospective cohort study looking at the impact of gastric sleeve versus gastric bypass showed no differences in BMI reduction and excess weight loss between the two groups in the first year after surgery.²⁷⁴ Changes in lipid profile at 1 year showed a significant decrease in LDL-C from baseline in the RNYGB group but not the LSG group. Both groups showed an increase in HDL-C levels, but this increase was greater in the LSG group. TG concentrations showed a similar decrease from baseline in both groups. Factors independently associated with LDL-C reduction were greater baseline total cholesterol and undergoing RNYGB. A greater increase in HDL-C was associated with LSG, older age, and baseline HDL-C. The authors of this study concluded that RNYGB produces an overall improvement in lipid profile, with a clear benefit in *all* measured lipid fractions. Although LSG did not alter LDL-C levels, its effect on HDL-C was comparable to or greater than that obtained with malabsorptive techniques.

In regard to gastric banding versus LSG and effects on metabolic parameters, one 2012 study evaluated concentrations of ghrelin, insulin, glucose, TGs, total and HDL-C, as well as aspartate aminotransferase and alanine aminotransferase levels in 200 patients who underwent

LAGB or LSG.²⁷³ The percentage of effective weight loss, effective BMI loss, concentration of ghrelin, insulin, glucose, TGs, total cholesterol, HDL-C, LDL-C, alanine aminotransferase, aspartate aminotransferase, and HOMA-IR values was taken preoperatively and at day 7, 1 month, and 3 and 6 months after surgery. Both after LSG and after LAGB, statistically significant reduction in BMI, serum insulin, glucose and HOMA-IR was noticed in comparison to the preoperative values. Post-LAGB, patients showed an increase of ghrelin, whereas after LSG those patients demonstrated a decrease in ghrelin. Correlations between glucose and BMI reduction, and between insulin and BMI reduction, in both cases were more favorable in the LSG group.

In summary, as with changes in lipid parameters with nutritional, physical activity, and drug interventions, bariatric surgeries associated with the greatest weight loss promote the greatest degree of changes in lipid parameters. Specifically, TG levels are substantially reduced, HDL-C levels are ultimately increased, and with substantial weight loss, LDL-C levels are significantly decreased as well (see Table 20 for a summary of metabolic changes associated with bariatric surgery procedures). Although it might be reasonably concluded that most of these effects are related to improvement in adiposopathic

Table 20 Summary of metabolic changes associated with bariatric surgery procedures

Lipid Parameter	RNYGB	LAGB	LSG
Total cholesterol	↓	↓/-	↓
TGs	↓	↓	↓
LDL-C	↓	↓	↓
VLDL	↓	↓	↓
HDL-C	↑	↑	↑
RLP-C	↓	?	?
apo E	↓	?	?
apo A-1	↓ → +/-	?	?
apo A-II	↓ → +/-	?	?
CETP mass	↑	?	?
CETP activity	↓	?	?
LCAT mass	↓	?	?
LCAT activity	↓	?	?
Adiponectin	↑	↑	↓
IL-6	↓	↓	?
CRP	↓	↓	?
HOMA-IR	↓	↓	↓
Leptin	↓	↓	↓
Ghrelin	↓	↓/↑/-	↓
GLP-1	↑	↑	↑
GIP	↓	↓	↑/?

apo, apolipoprotein; CETP, cholesterol ester transfer protein; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon like peptide-1; HOMA-IR, homeostatic model assessment-insulin resistance; IL-6, interleukin-6; LCAT, lecithin cholesterol acyltransferase; LDL-C, low-density lipoprotein cholesterol; RLP-C; remnant-lipoprotein cholesterol; TGs, triglycerides; VLDL, very-low-density lipoprotein.

dysmetabolism that so often accompanies the increase in body fat, it is also probable that many of these favorable lipid effects are related to unique hormonal changes accompanying bariatric surgery.

Executive summary/evidence based key points

- Adiposopathy is an important contributor to the dyslipidemia epidemic and other metabolic disease epidemics such as T2DM, high blood pressure, and CVD.
- Adipose tissue is a body organ that is integral to essential endocrine and immune functions affecting lipid levels.
- An increase in caloric balance among genetically and environmentally susceptible patients causes adipocyte and adipose tissue dysfunction (adiposopathy), which may promote dyslipidemia.
- “Adiposopathic dyslipidemia” is characterized by increased TG, reduced HDL-C, increased small dense LDL particles, and increased lipoprotein remnant lipoprotein levels, and often occurs in overweight patients with visceral adiposity and fatty liver.

Lipid-induced insulin resistance

- The development of insulin resistance in adiposity is closely associated with ectopic lipid accumulation, specifically DAG.
- In skeletal muscle, DAG mediated activation of PKC θ impairs insulin-stimulated muscle glucose transport.
- In the liver, DAG-mediated activation of PKC ϵ diminishes the ability of insulin to promote glycogen synthesis and inhibit gluconeogenesis.
- Therapies that decrease ectopic lipid accumulation may improve insulin resistance and potentially valuable in treating metabolic syndrome and T2DM.

Adipose tissue dysfunction as a contributor to the metabolic syndrome

- A great many nonobese individuals, particularly from racial minority groups, are not recognized as having the metabolic syndrome and elevated risk for T2DM and CVD because of current focus on adipose tissue mass alone.
- Adipose tissue ENPP1 is involved in the regulation of adipocyte maturation. Lack of appropriate ENPP1 down-regulation in adipose tissue during weight gain is associated with adipose tissue dysfunction, increased plasma free fatty acids, systemic insulin resistance, and other components of the metabolic syndrome.

Adiposity and TGs

- Adiposity is often accompanied by a complex interaction of insulin resistance, genetics, diet, energy balance, and other factors leading to disordered metabolism of TG-rich lipoproteins.

- Adiposity and insulin resistance are common “second hits” in genetically and environmentally susceptible individuals potentially leading to severe hypertriglyceridemic dyslipidemias.
- Modest hypertriglyceridemia in the setting of adiposity is often associated with increased concentrations of small dense atherogenic LDL particles and TG-rich remnant lipoproteins, and is associated with heightened risk for atherosclerotic disease.
- T2DM, CVD, and steatohepatitis are common outcomes in adiposity complicated by hypertriglyceridemia.
- Adiposity with hypertriglyceridemia is common, frequently occurring in the setting of the metabolic syndrome. Identifying the lipoproteins in excess and severity of TG elevation is best accomplished by measurement of serum TG and apo B levels.
- Very high TG levels, >500 and more typically >1000 mg/dL, are associated with an increased risk of pancreatitis, usually due to inability to clear chylomicrons from serum, severe elevations in VLDL levels, or both.
- Moderately elevated TG levels are frequently associated with risk for vascular disease secondary to increased levels of atherogenic apo B-containing lipoproteins.
- T2DM, NAFLD, deterioration of vascular mechanics, and an increase in all-cause mortality are late consequences of chronic insulin resistance and hypertriglyceridemia.

Adiposity and HDL

- HDL-C is a highly validated predictor of CV risk and reductions in serum levels of this lipoprotein are a defining feature of the metabolic syndrome/insulin resistance.
- A low HDL-C in a background of insulin resistance is associated with greater CV risk than a low HDL-C in individuals who have normal insulin sensitivity.
- Insulin resistance and heightened systemic inflammation stemming from increased adiposity are associated with adverse changes in the HDL proteome and HDL metabolism, yielding reduced biosynthesis and increased catabolism.
- Renal function significantly impacts serum HDL-C; the glomerular hyperfiltration that can be observed among patients with adiposity, insulin resistance, or T2DM may exacerbate hypoalphalipoproteinemia.
- The reduction in serum levels of HDL-C may exacerbate hyperglycemia and insulin deficiency since islet cells appear to require exposure to HDL-C in order to synthesize and secrete insulin.
- No adequate outcomes data exist with which to recommend pharmacologic intervention for low HDL-C in the setting of adiposity and insulin resistance.
- Exercise, weight loss, and smoking cessation are associated with significant increases in serum HDL-C and should always be encouraged and likely constitute the best approach toward raising HDL-C in obese patients with or without insulin resistance.

Adiposity and LDLs

- LDL-C plasma concentrations tend to increase with increasing body weight in those <30 years of age, even among those who are not significantly overweight. LDL-C increases in middle-aged patients with a BMI of up to about 28 kg/m². An increase in fasting TG levels is a consistent finding in overweight and obese persons.
- The cholesterol content of LDL particles often decreases with weight gain. However, a concomitant increase in the number of LDL particles results in little change in the observed LDL-C. LDL particles and apo B increase far more when TG exceeds 150 mg/dL, but measured LDL-C tends not to increase.
- HDL-C and HDL particle number tend to decrease with weight gain.
- Weight loss in obese individuals produced by diet, drugs, or bariatric surgery reduces TG and increases HDL-C concentrations but frequently produces minimal change in LDL-C levels. The total number of LDL (apo B containing) particles usually falls with weight loss and the cholesterol content per particle rises. The HDL particles and their cholesterol content tend to increase. A fall in plasma TG rich lipoproteins appears to drive these changes through reduced CETP activity.
- From a lipid standpoint, the risk of vascular disease events correlates best with an increase in LDL particle or apo B concentration.

Principles of bariatric endocrinology

- Adipose tissue is biologically active and contributes to metabolic homeostasis.
- Adipose tissue anatomical changes, and the development of dysfunction caused by accumulation of regional fat mass, constitute adiposopathy.
- Adiposopathy is etiologic in the development of metabolic derangements that are established cardiovascular risk factors.
- The use of BMI alone to stratify metabolic risk has limited clinical application.
- Measurements of intra-abdominal or visceral fat mass are good clinical markers of adiposopathy.
- The dyslipidemia of adiposopathy is best managed with effective interventions that, along with total fat reduction, also result in intra-abdominal fat mass reduction.

Nutrition, weight loss, and lipids/lipoproteins

- TG levels are among the lipid parameters most likely to respond to nutritional intervention. Greater baseline TG levels typically have the potential for greatest reduction with nutrition-derived weight loss in overweight patients.
- The type of nutritional intervention also is of significance in that weight loss achieved in overweight patients by lower-carbohydrate diets would be expected to lower TG more than weight loss achieved by higher-carbohydrate diets.

- During weight loss, LDL-C typically decreases followed by: (1) some increase compared with baseline levels; (2) return to baseline levels; or (3) a sustained reduction. These varied responses may be related to the nutrient profile of the diet consumed after weight loss, and/or weight loss maintenance or weight regain after weight loss.
- HDL-C is affected by weight loss and the composition of the weight loss diet. Higher-carbohydrate/low-fat diets decrease HDL-C whereas higher-protein/lower-carbohydrate diets maintain or increase HDL-C.

Physical activity, weight loss, and dyslipidemia

- Exercise training of sufficient quantity can reduce adiposity with or without weight loss.
- Although not always true, in general, fat weight reduction is required for exercise generated total cholesterol and LDL-C reduction.
- Exercise intervention provides potential advantages to dietary-only intervention. Exercise induces greater insulin action and insulin sensitivity, particularly when matched for energy-equivalent dietary restriction. Sufficient physical activity also prevents the decrease in the resting metabolic rate typically associated with weight loss by energy restriction alone. Also, when exercise training is added to dietary weight loss, there is a preferential reduction in subcutaneous abdominal adipocyte size, and intramuscular TG and visceral adipose tissue.
- Overweight and obese adults should progress to a minimum of 150 minutes of moderate intensity exercise per week and, when possible, progress to >200 minutes of moderate intensity exercise per week.

Drug therapies

- Weight-management drug therapy may not only improve the weight of patients but may also improve the health of patients, including patient lipid levels.
- The lipid parameter most consistently susceptible to improvement with weight loss is the reduction in TG levels, which is the lipid parameter most associated with adiposopathic dyslipidemia. Greater weight loss is often required to reduce LDL-C levels.
- Given that the effectiveness of TG-lowering agents is greatest among patients with the greatest baseline levels, studies of weight management agents in patients with hypertriglyceridemia are needed.
- At the very least, post-hoc analyses of existing trials in patients with higher and lower baseline TG levels (such as tertile analyses) would be helpful to lipidologists and clinicians who manage overweight hypertriglyceridemic patients.
- In overweight patients, a loss of approximately 5% of body weight can improve adipocyte and adipose tissue function in patients with adiposopathy, with a consequence that a loss of only about 5% to 10% of body

weight can improve metabolic diseases such as dyslipidemia.

- Most weight-loss drug therapies do not typically result in substantial changes in HDL-C and LDL-C levels, which is similar to responses to modest exercise alone.

Impact of bariatric surgery and weight loss on lipids

- Bariatric surgery is becoming a more frequently used treatment for adiposity. This is occurring not only to reach BMI targets, but also to improve metabolic parameters such as lipid fractions, plasma lipoprotein levels, reduce inflammatory markers, as well as improve insulin sensitivity.
- RNYGB, LAGB, and LSG are the most commonly performed procedures, each of which has different anatomic and physiologic properties.
- The most evidence thus far supports surgical procedures that by-pass the stomach (eg, RNYGB) as superior for achieving loss of excess body weight as well as improvement in lipid profile, which are likely due a combination of reduction in body fat, as well as due to alterations in gut and other hormones and inflammatory factors.
- The more recent procedures such as LAGB and LSG have favorable metabolic and lipid consequences as well due to gastric restriction, a change in gut hormone levels, and reduction in inflammatory markers.

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