# Obesity, Hypertension, and Dyslipidemia

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## Contents



**Abstract**

Hypertension and dyslipidemia are closely related with obesity. Obesity releases nonesterified fatty acids into the circulation, increasing fasting plasma triglycerides, reducing high-density lipoprotein cholesterol, and inducing a shift to a pro-atherogenic composition (small, dense) of low-density lipoproteins. Obesity activates the sympathetic nervous system, increases sodium and water reabsorption, and increases the production of angiotensin II factors that determine hypertension shift in obese people.

**Keywords**

Obesity · Hypertension

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| Abbreviations | |
|---|---|
| 24 h ABPM | 24 hour ambulatory blood pressure monitoring |
| Ang | Angiotensin; RAS: Rennin–Ang system |
| BMI | Body Mass Index |
| BP | Blood pressure |
| FFAs | Free fatty acids |
| HDL | High-density lipoprotein |
| IDL | Intermediate density lipoproteins |
| LDL | Low-density lipoprotein |
| MAG | Monoacylglycerol |
| MetS | Metabolic syndrome |
| NAFLD | Non-alcoholic fatty liver disease |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 |
| PLs | Phospholipids |
| SNS | Sympathetic nervous system |
| TAG | Triacylglycerol |
| TG | Triglycerides |
| VLDL | Very low density lipoproteins |

## Introduction

The prevalence of obesity doubled between 1980 and 2008, affecting not only high but also middle- and low-income countries. Obesity and modern life style includes a shift from the labor and agricultural work to sedentary jobs and the lack of physical exercise with increase in caloric intake as prepared out of house food typically includes more sugar and trans lipids compared to home meals. Children and adolescents watch more TV and exercise less as outside physically active play has been replaced with video games.

Obesity is associated with hypertension, type II diabetes mellitus, heart failure, dyslipidemia, chronic kidney disease, and cancer (Mancia et al. 2013; Kotsis et al. 2005; Nagarajan et al. 2016). According to the World Health Organization (WHO) 44% of the prevalence of diabetes, 23% of the prevalence of ischemic heart disease, and 7–41% of certain types of cancer are attributable to obesity. Metabolic syndrome (MetS) includes abdominal obesity, high blood pressure, elevated plasma glucose levels (insulin resistance and type II diabetes mellitus), high serum triglycerides, and low high-density lipoprotein (HDL) levels. The exact definition of the metabolic syndrome differs between various organizations, but its importance and relationship to type 2 diabetes is evident. Obesity is often accompanied by obstructive sleep apnea syndrome (Bibbins-Domingo et al. 2017) and nonalcoholic fatty liver disease (NAFLD) that are considered as additional risk factors for cardiovascular disease (Kalia and Gaglio 2016). Abdominal obesity is associated with reduced insulin-mediated glucose muscle uptake causing hyperinsulinemia and insulin resistance that linked to increased cardiovascular risk factors. The cardiometabolic syndrome is very

important since heart attacks and strokes are the major causes of the high mortality rates in type 2 diabetic patients, and the need for prevention is increased in such patients. Thus, obesity has evolved from a social problem to a severe health problem.

The relationship between obesity and hypertension is well established both in children and adults in different populations and ethnic groups (Kotsis et al. 2005; Stabouli et al. 2005; Bramlage et al. 2004; Baik et al. 2000). Normal weight was reported in 58.1% of true normotensive subjects (confirmed both with office and 24 h ABMP), while obesity was found in 43.7% of the true hypertensive subjects. In patients followed up by primary care physicians, the prevalence of hypertension was increased from 34.3% in the normal weight population to 74.1% in the obesity population (Bramlage et al. 2004). Cardiovascular disease mortality among men aged <65 years increased linearly with greater body mass index (Baik et al. 2000).

Obesity is associated with impaired lipid metabolism. Insulin resistance and lipolysis induce free fatty acid (FFA) release that increase fasting plasma triglycerides (TG), and decrease high-density lipoprotein (HDL) cholesterol and shift low-density lipoproteins (LDL) to a more proatherogenic composition (small, dense LDL) (Franssen et al. 2011). According to the latest guidelines of European Society of Cardiology/European Society of Atherosclerosis, the target of lipid metabolism is focused on LDL. Patients having low to moderate risk should have LDL levels below 115 mg/dl, in high-risk patients LDL target is below 100 mg/dl, and in very high-risk patients the target is below 70 mg/dl (Catapano et al. 2016). Despite that LDL quantity is the main target in patients with hyperlipidemia, the residual risk from increased TG and low HDL and LDL quality should not be underestimated especially in obese subjects.

## Obesity-Induced Hypertension

Sympathetic nervous system, renal mechanisms, inflammation, and hormones such as leptin, insulin, corticosteroids, and the renin-aldosterone angiotensin system seem to have a key role in obesity-induced hypertension (Kotsis et al. 2010). The interaction of these mechanisms with behavioral aspects such as salt and potassium intake, and physical exercise plays an important role in obesity-induced hypertension.

Electronic medical records from children and adolescents in the USA examined data from a population of 117,618 children and adolescents aged 6–17 years with measured height, weight, and blood pressure. The proportion of children with normal blood pressure fell, while those with prehypertension or hypertension increased as BMI percentage increased above the obesity threshold, suggesting that obesity early in life is associated with increased BP. Severe obese children compared to moderately obese children have a threefold increased risk of hypertension (Lo et al. 2014). Data from the Framingham Heart Study, a population-based prospective cohort study, confirm the increased prevalence of hypertension in obese subjects. Participants from the Offspring and Third Generation studies were analyzed

and the prevalence of hypertension was increased from 11.5% in normal weight subjects to 22.8% in overweight and 37.6% in the obese group. The prevalence of hypertension increased significantly with increasing BMI category (Molenaar et al. 2008).

## Mechanisms of Obesity-Induced Hypertension

The sympathetic nervous system (SNS) seems to be activated in obesity. High-energy intake increases norepinephrine turnover in peripheral tissues, raises resting plasma norepinephrine concentrations, and amplifies the rise of plasma norepinephrine in response to stimuli such as upright posture. Peripheral α1- and β-adrenergic receptors also found to be stimulated contributing to the elevated sympathetic activity. Pharmaceutical blockade of α and β adrenergic system reduced blood pressure levels in obese animal models and human studies (Landsberg and Krieger 1989).

Increased levels of circulating FFAs in obese populations enhance vascular α-adrenergic sensitivity and increase α-adrenergic tone. Lysophospholipids and FFAs inhibit Na+, K + −ATPase, and the sodium pump, raising vascular smooth muscle tone and resistance. Na/K-ATPase is binding with lysophospholipids and FFAs, the epidermal growth factor receptor is activated and reactive oxygen species are increasingly produced (Stepniakowski et al. 1995).

Increased sodium and water excretion through pressure natriuresis and diuresis is the first renal mechanism in the development of hypertension in obese people. If excretion exceeds intake, extracellular-fluid volume decreases reducing venous return and cardiac output. Renal blood flow consequently decreases, and the kidney retains salt and water until arterial pressure returns to normal. During the early stages of obesity, before loss of nephron function secondary to glomerular injury, primary sodium retention occurs because of an increase in renal tubular reabsorption. Extracellular-fluid volume is expanded because of volume overload. Sympathetic activation appears to mediate at least part of the obesity-induced sodium retention and hypertension since adrenergic blockade or renal denervation markedly attenuates these changes. Recent observations suggest that leptin actions in the hypothalamus may link excess weight gain with increased sympathetic activity (Hall et al. 2000). High fat diet in conscious dogs increases rennin activity, while fat restriction has the opposite effects. Under normal conditions, RAS represents a regulatory mechanism, which prevents extreme variations in arterial pressure (especially very low values) that may reduce organ perfusion, while high salt intake reduces the production of Ang II (Hall 1997).

Adipose tissue has important paracrine physiology. Adipose tissue-derived angiotensinogen may enter the circulation having systematic actions or may have local actions at the perivascular adipose tissue. Renin, Ang II, angiotensinogen, and Ang II receptors are found in abundance in adipose mass suggesting that a local tissue Ang system is settled at adipocyte level. The tissue RAS and the circulating RAS are in a state of constant interaction. Angiotensinogen locally produced is taken

up by the cells that Ang II receptors are over expressed. Angiotensinogen production leads to elevation of BP through the actions of Ang II, which induce systematic vasoconstriction, direct sodium and water retention, and increased aldosterone production (Campbell 1987). Studies in patients under sodium restriction, which activates the RAS system, provided evidence for a presynaptic potentiating effect of Ang II on sympathetic neurotransmission (Taddei et al. 1995).

The renal effects of obesity include both structural and functional adaptations, such as increased glomerular filtration rate, increased renal blood flow, and renal hypertrophy. Patients with obesity have increased filtration fraction with a role for afferent arteriolar dilation in the mediation of the increased trans-capillary hydraulic pressure gradient. Elevation in GFR may be mediated in part by increased protein consumption and increased tissue blood flow need. Weight gain has been associated with an expanded renal medullary interstitium in humans and in animal models of obesity. Physical compression of both kidneys is generated from the accumulation of adipose tissue around the organs, a fact that demonstrates the vital role of visceral obesity in the development of renal disease. Deposition of extracellular matrix throughout the renal medulla is expanded, and the tissue surrounding the ducts of Bellini at the vascular pole tends to prolapse. Lipids and proteoglycans compress the renal parenchyma toward the pole of the kidney resulting in the formation of round-shaped, enlarged kidneys in obese subjects (Dwyer et al. 2000). The primary histologic features are relatively few lesions of focal segmental glomerulosclerosis, profound glomerular enlargement due to glomerular hyalinosis and fibrosis, as well as lipid accumulation in the glomeruli and adhesion to Bowman's capsule. Despite the observed high incidence of glomerulomegaly, glomerular changes in obesity-induced renal injury are incomparable with those of diabetic nephropathy, mainly because of the lower severity of changes in the mesangial space. Other causes of renal injury, apart from high-fat intake, could possibly include overexpression of Ang II with a consequent increase in proliferative factors such as transforming growth factor-b and plasminogen activator inhibitor, high protein diet, as well as hyperinsulinemia (Kambham et al. 2001). Mechanisms of obesity-induced hypertension are summarized in Fig. 1.

## Hormones Related to the Obesity-Induced Hypertension

Obesity and insulin resistance are two well-connected conditions. Normally, insulin exhibits a sodium-retaining effect through its direct action on the renal tubules. A potential enhancement of sodium retention because of acute hyperinsulinemia could increase blood pressure in obese patients, but in chronic hyperinsulinemia this mechanism has no significant effect on blood pressure regulation. Insulin is also reported to acutely increase SNS activity and norepinephrine levels in both normotensive and hypertensive subjects, but the main action of insulin is peripheral vasodilation that is mediated by a β-adrenergic mechanism (Anderson et al. 1992; Hall 1993).

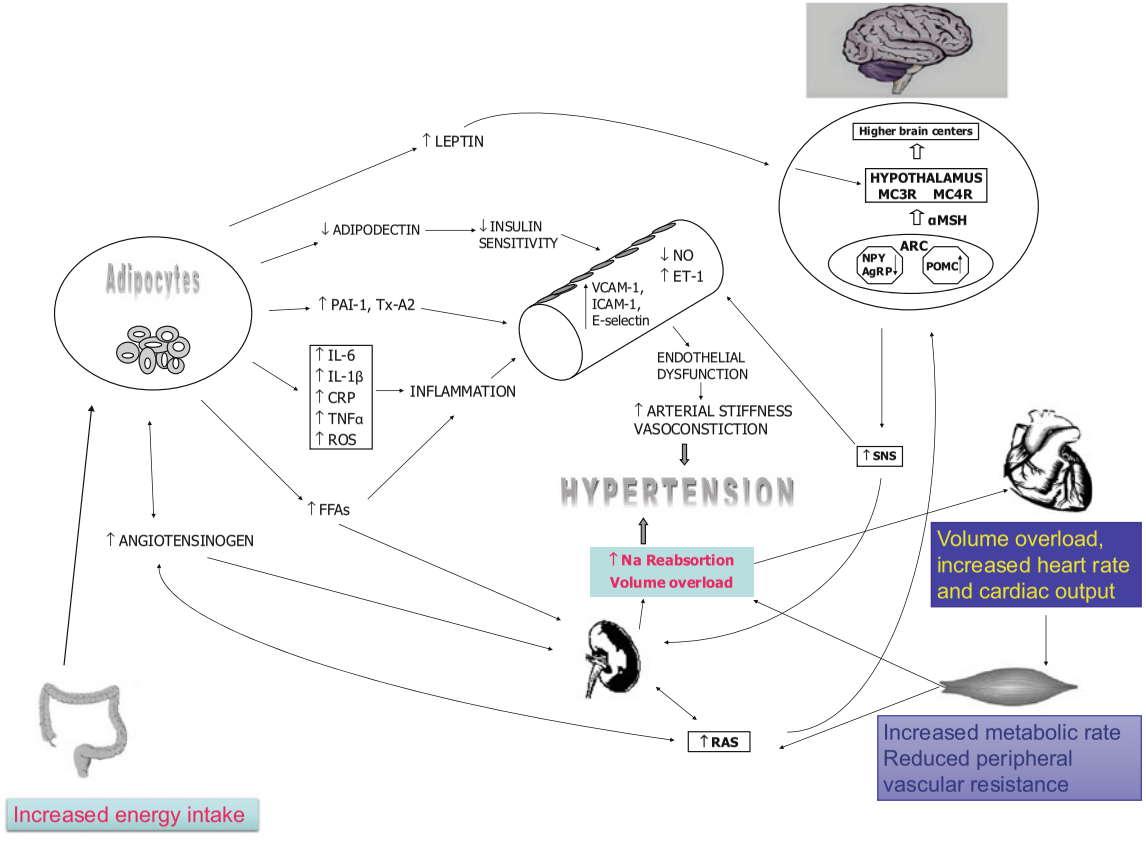


**Fig. 1** Mechanisms of obesity-induced hypertension (Modified from Kotsis et al. 2010)

Leptin is a peptide hormone secreted from adipose tissue that activates the sympathetic nervous system in animal models. Leptin plays a physiological role in thermogenesis, energy expenditure, and by decreasing food consumption. Leptin is bound to its short-form receptors and transported across the blood–brain barrier to the arcuate nucleus to modulate appetite controlling feedback mechanisms of neuropeptides. Studies in animals and humans with leptin deficiency show high incidence of obesity but absence of hypertension. Leptin deficiency in the $Lep^{ob/ob}$ mouse leads to early-onset of obesity, hypercorticosteronemia, hyperglycemia, hyperinsulinemia, and hypothyroidism (Schubring et al. 1999). Besides the high body weight, $Lep^{ob/ob}$ mice are hypotensive (Mark et al. 1999). Leptin deficiency in human is also associated with similar metabolic abnormalities but normal blood pressure (O'Rahilly 2009), whereas increased leptin levels have been reported in essential hypertension (Agata et al. 1997). Obesity without hypertension is a characteristic of the melanocortin 4 receptor (MC4-R) null mouse. The MC4-R deficiency in mouse is related to obesity, hyperglycemia, hyperinsulinemia, and hypometabolism. Despite obesity MC4-R-deficient mice are not hypertensive (Sutton et al. 2006).

In obese humans selective resistance of leptin actions has been reported, and despite high leptin levels there is no reduction in food intake or increase in energy expenditure, while the SNS stimulation is still present (Correia et al. 2002). Neuropeptide Y is a neurotransmitter, expressed in the hypothalamic arcuate nucleus at high rates during fasting. Its orexigenic action is combined with reduction in thermogenesis and downregulation of the sympathetic neurons. Normally, its expression is suppressed by high leptin levels. In the leptin-resistant state, neuropeptide Y should rather be considered overexpressed acting as a vasoconstrictor and could have a role in the obesity-related hypertension (Lundberg et al. 1987). Glucocorticoids increase food intake, reduce energy expenditure, and promote insulin resistance, fat accumulation, and hypertension. Obese rodent models of obesity, which are characterized by hypercorticosteronemia, restore their lower body weight after adrenalectomy that is regained with glucocorticoid replacement treatment (Saruta 1996). Obese individuals have increased adipose levels of 11b–hydroxysteroid dehydrogenase-1,72,73, an enzyme that regenerates active cortisol from the inactive 11-keto forms. The aP2-HSD1 mice overexpress the enzyme in fat cells and develop obesity, insulin resistance, dyslipidemia, and hypertension. These mice have increased sensitivity to dietary salt and increased plasma levels of angiotensinogen, Ang II, and aldosterone (Masuzaki et al. 2003). These reports suggest that a local activation of glucocorticoid production in the adipose tissue induce an activation of the RAS, which mediates a salt-sensitive form of hypertension in obesity.

Finally, there are people with obesity who are protected from hypertension. Ethnicity plays a role in the development of obesity-induced hypertension. The Pima Indians of Arizona have the highest reported prevalence of obesity in the world, but a relatively low prevalence of hypertension and atherosclerotic disease (Saad et al. 1990). The lack of increase in muscle sympathetic nervous activity (MSNA) with increasing adiposity and insulinemia in Pima Indians may explain, in part, why this population has a low tendency for hypertension, despite the high prevalence of obesity.

## Obesity-Induced Dyslipidemia

Conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention, NHANES III was designed to provide USA national representative data estimating the prevalence of major diseases. Approximately 63% of men and 55% of women aged 25 years or older in the US population were overweight or obese and 21% of men and 27% of women were obese suggesting that 1 to 4 US citizens were obese between 1990 and 2000. High blood pressure was the most common overweight- and obesity-related health condition and its prevalence showed a strong increase with increasing weight status category. In obese subjects the prevalence of hypertension was more than 40% and followed closely by high cholesterol levels with a prevalence of more than 35% in both gender, while the prevalence of diabetes was lower around 10–15% depending on the gender and the severity of obesity. Among younger men and women cholesterol levels of overweight and obese were elevated compared with the normal weight group, but there was no evidence of a gradient increase with weight status category, as seen in hypertension status, suggesting that severe obese did not have the highest lipid levels. Among older subjects, cholesterol levels were significantly increased only in overweight individuals (Must et al. 1999). In women using linear trend analysis, changes in BMI from normal weight to overweight categories of BMI was associated with higher TG levels and lower HDL levels independently of their menopausal status. Overweight in premenopausal women was found to be associated with 18 mg/dL higher total cholesterol levels, 26 mg/dL higher non-HDL levels, and 17 mg/dL higher LDL levels compared to normal weight women (Denke et al. 1994). In young men BMI increase from normal weight to overweight was associated with increased total cholesterol levels by 23 mg/dL, non-HDL levels by 27 mg/dL, and LDL levels by 23 mg/dL. For middle-aged and older men, the same change in BMI was associated with smaller but still significant differences in triglycerides and HDL cholesterol levels, whereas the LDL cholesterol levels were unchanged (Denke et al. 1993). The typical dyslipidemia of obesity consists of increased TG and FFA, decreased HDL, and normal or slightly increased LDL, with increased small dense LDL. The concentrations of plasma apolipoprotein B are also often increased, partly due to the hepatic overproduction of apo B containing lipoproteins.

## Lipoprotein Metabolism

Dietary fats consist of triacylglycerol (TAG) (90–95% of the total energy derived from dietary fat), phospholipids (PLs), sterols (mainly cholesterol, β-sitosterol), and fat-soluble vitamins. Although β-sitosterol accounts for 25% of dietary sterols, it is not absorbed by humans under physiological conditions (Iqbal and Hussain 2009). The digestion of lipids begins in the oral cavity through exposure

to lingual lipases and continues in the stomach through the effects of both lingual and gastric enzymes. TAG is digested primarily by pancreatic lipase in the upper segment of the jejunum. The activity of pancreatic lipase on the sn-1 and sn-3 positions of the TAG molecule results in the release of 2-monoacylglycerol (2-MAG) and free fatty acids (FFAs), which are uptake by the enterocytes via passive diffusion and specific transporters. Further hydrolysis of 2-MAG (by pancreatic lipase) results in the formation of glycerol and FFAs (Pan and Hussain 2012). The specific cholesterol transporter Niemann-Pick C1 Like 1 protein (NPC1L1) is responsible for taking up the cholesterol by the enterocytes (Davis et al. 2004). MAG and free fatty acids are first converted to diacylglycerol (DAG) by acyl coenzyme A monoacylglycerol acyltransferase (MGAT) enzymes. DAG is then converted to TAG by acyl coenzyme A diacylglycerol acyltransferases 1 and 2 (DGAT1 and DGAT2). TAG is also synthesized from glucose by the glycerol-3-phosphate pathway. In this pathway, three isoforms of phosphatidic acid phosphohydrolase (PAPase, also known as lipins 1–3) hydrolyze the phosphate to form DAG, which finally synthesizes TAG as in the MAG pathway (Takeuchi and Reue 2009).

Cholesterol-esters and TG are packed together with phospholipids and apolipoprotein (apo) B48 to form chylomicrons, which are gradually converted into chylomicrons remnants and are delivered into the liver. The liver synthesizes TG-rich lipoproteins called very low-density lipoproteins (VLDL). Apo B100 is the structural protein of VLDL, which is secreted by the liver and transports intermediate density lipoproteins (IDL) and LDL (Klop et al. 2012). Chylomicrons and VLDL change form during lipolysis to produce chylomicron remnants and dense LDL, respectively. Chylomicron remnants are uptaken again by the liver and LDL is primarily uptaken by the liver via the LDL receptor. The LDL receptor is regulated by the proprotein convertase subtilisin/kexin type 9 (PCSK9). When PCSK9 is bound to the LDL receptor, then the LDL receptor is destroyed due to degradation. In contrast, when PCSK9 is absent LDL receptor is recycled back to the surface of the hepatocytes (Lambert et al. 2012).

The small intestine plays a role for the cholesterol uptake and delivery in the circulation. Intestinal apolipoprotein A-1 acceptor molecule (ABC1A1), which is synthesized from enterocytes and hepatocytes, seems to be responsible for the intestinal cholesterol mobilization and HDL formation and constitutes the main form of HDL. HDL promotes the uptake of cholesterol from peripheral tissues and returns cholesterol to the liver. The cholesterol within HDL is changed into cholesterol-esters by HDL-associated lecithin-cholesterol acyltransferase (LCAT), while cholesterylester transfer protein (CETP) and phospholipid transfer protein (PLTP) are responsible for the same procedure for the HDL particles in the circulation. At this stage, HDL requires TG from TG-rich lipoproteins in exchange for cholesterol-esters as a direct consequence of the CETP action. In the liver, hepatic lipase hydrolyses HDL-associated TG and also phospholipids induce the formation of smaller HDL particles, which can contribute again to the reverse cholesterol transport (Klop et al. 2012).

## Obesity and Lipoproteins

Obesity is the result of excessive energy intake and low energy expenditure. Adipose tissue is now recognized as an important secretory organ releasing into the circulation many peptides that affect metabolism. Increased adipose tissue mass increase FFA into the circulation. FFA release from adipose tissue is suppressed by insulin in both lean and obese individuals, but in obesity the process is insulin resistant. FFA release per unit fat mass is less in subjects with obesity than in those who are lean. However, because of the increased fat mass, total FFA delivery to the circulation is increased in obesity. Despite high plasma insulin concentrations in response to a standard meal, obese subjects fail to suppress FFA release from adipose tissue. Increased availability of fatty acids will decrease glucose utilization in muscle and stimulate hepatic glucose production. Elevated FFA also increases pancreatic β-cell accumulation of lipids which may be a part of the link between obesity, insulin resistance, and development of type 2 diabetes. Adipose tissue is an important site for the disposal of dietary triacylglycerol in the postprandial period. Obesity is typically characterized by increased postprandial lipemia, reflecting at least in part prolonged circulation of dietary fatty acids. These fatty acids will be removed by several tissues, including skeletal muscle, pancreas, and liver instead of adipose tissue. In obesity, adipose tissue overloaded with TAG has reduced buffering capacity for lipid storage in adipocytes. Fat cells fail in their normal role to protect other tissues from the daily influx of dietary fatty acids (Frayn 2001; Pan et al. 1997; Byrne et al. 1991). Lipolysis of TG-rich lipoproteins is impaired in obesity by reduced mRNA expression levels of LPL in adipose tissue (Clemente-Postigo et al. 2011), reductions in LPL activity in skeletal muscle, and competition for lipolysis between VLDL and chylomicrons. The increased synthesis of VLDL in the liver can inhibit lipolysis of chylomicrons, which promotes hypertriglyceridemia (Klop et al. 2012).

The free VLDL particles undergo enzymatic exchanges with other lipoprotein particles such as HDL and LDL, via cholesterylester transfer protein (CETP). Once these TG-rich lipoprotein particles are exposed to various lipases, then the HDL particles become smaller and undergo metabolism and excretion by the kidney, resulting in decreased HDL levels. In the presence of hypertriglyceridemia, the cholesterol-ester content of LDL decreases, whereas the TG content of LDL increases by the activity of CETP. The increased TG content within the LDL is hydrolyzed by hepatic lipase, which leads to the formation of small, dense LDL particles. Small dense LDL are relatively slowly metabolized with a 5-day circulating time, which promotes its atherogenicity. The VLDL particles undergo also lipolysis, resulting in VLDL remnants and consequently formation of small, dense LDL particles (Klop et al. 2013). Lipoprotein obesity-induced dyslipidemia mechanisms are shown in Fig. 2.

Inflammation has a special role in obesity-induced dyslipidemia. Macrophage, TNF-α, IL-6, IL-1, and serum amyloid A (SAA) may promote dyslipidemia (Gutierrez et al. 2009). The presence of macrophages in adipose tissue increases in obesity. Obese people have higher macrophage infiltration into adipose tissue compared to thin people, and this is correlated with higher TGs and lower HDL

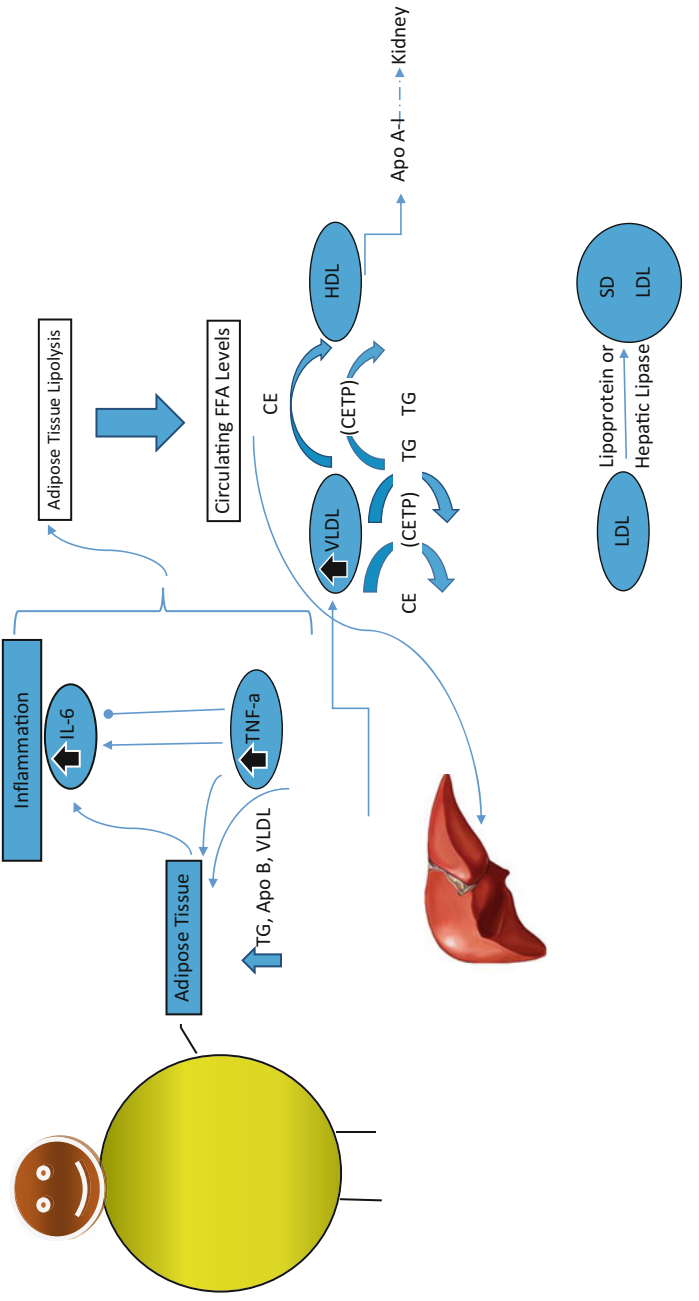


**Fig. 2** Obesity and lipoprotein metabolism

(Huber et al. 2008). A macrophage-specific marker (*CD68*), most found in subcutaneous adipose tissue, is also positively correlated with plasma-free fatty acid as well as LDL and negatively correlated with HDL levels (Huber et al. 2008). TNF-α was found positively correlated with hypertriglyceridemia and VLDL not only in animals but also in humans (Mohrschladt et al. 2000). After increasing TNF-α levels in the circulation of hamsters TG-rich particles increased, while increased serine phosphorylation of insulin receptor substrate-1 and elevated apo B48 production may further increase plasma TGs and exacerbate dyslipidemia (Qin et al. 2008). IL-6 is also associated with hypertriglyceridemia and negatively with serum HDL-cholesterol levels (Jonkers et al. 2002). The administration of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1, also reduces expression of Apo A1 in hepatic cells and plasma. Apo A1 is responsible for HDL structure and low concentrations of apoA1 are independent predictors for the presence and severity of cardiovascular disease (Hardardottir et al. 1994). IL-10 has different actions; increased IL-10 levels are associated with increased plasma triglyceride levels, but decreased total cholesterol and LDL levels (van Exel et al. 2002). SAA an acute-phase protein that is produced in the liver, in adipose tissue, intestinal epithelial cells, and macrophages is an apolipoprotein that can replace apolipoprotein A1 (apoA1) as the major HDL apolipoprotein and found increased in subcutaneous white adipose tissue of obese patients. The role of SAA protein in regulating gene expression related to lipid metabolism shows increased inflammatory cytokine gene expression (IL-6 and TNF-a) and glycerol release indicating increased lipolysis by decreasing the expression of perilipin, a lipid droplet–protective protein, which would then allow an increase in hormone-sensitive lipase activity (O'Brien and Chait 2006; Poitou et al. 2005; Chen et al. 2008).

Adiponectin has the opposite effect on dyslipidemia compared to TNF-a, IL6, and IL-1, and its increase is correlated with increased HDL levels and decreased triglycerides and LDL levels. Adiponectin acts directly to lipoprotein lipase, enhancing VLDL clearance and reducing plasma triglyceride levels. Adiponectin activates 5triphosphate-activated protein kinase (AMPK) in the liver, an action that marks the beginning of a sequence of reactions. AMPK inhibits acetyl coenzyme A carboxylase (ACC), and this coenzyme decreases the concentration of malonyl CoA, which is finally responsible for the increase of free fatty acids (Yamauchi et al. 2002). Moreover, its action is based on mRNA expression and secretion of apo A1, suggesting that adiponectin might increase HDL in the liver (Oku et al. 2007).

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