



Review

# Obesity-Related Changes in High-Density Lipoprotein Metabolism and Function

Julia T. Stadler \* and Gunther Marsche \*

Otto Loewi Research Center, Division of Pharmacology, Medical University of Graz, 8010 Graz, Austria

\* Correspondence: julia.stadler@medunigraz.at (J.T.S.); gunther.marsche@medunigraz.at (G.M.);

Tel.: +43-385-74115 (J.T.S.); +43-316-385-74128 (G.M.)

Received: 30 October 2020; Accepted: 24 November 2020; Published: 26 November 2020



**Abstract:** In obese individuals, atherogenic dyslipidemia is a very common and important factor in the increased risk of cardiovascular disease. Adiposity-associated dyslipidemia is characterized by low high-density lipoprotein cholesterol (HDL-C) levels and an increase in triglyceride-rich lipoproteins. Several factors and mechanisms are involved in lowering HDL-C levels in the obese state and HDL quantity and quality is closely related to adiponectin levels and the bioactive lipid sphingosine-1-phosphate. Recent studies have shown that obesity profoundly alters HDL metabolism, resulting in altered HDL subclass distribution, composition, and function. Importantly, weight loss through gastric bypass surgery and Mediterranean diet, especially when enriched with virgin olive oil, is associated with increased HDL-C levels and significantly improved metrics of HDL function. A thorough understanding of the underlying mechanisms is crucial for a better understanding of the impact of obesity on lipoprotein metabolism and for the development of appropriate therapeutic approaches. The objective of this review article was to summarize the newly identified changes in the metabolism, composition, and function of HDL in obesity and to discuss possible pathophysiological consequences.

**Keywords:** obesity; HDL-C; HDL subclasses; cholesterol efflux; adiponectin; sphingosine 1-phosphate; bariatric surgery

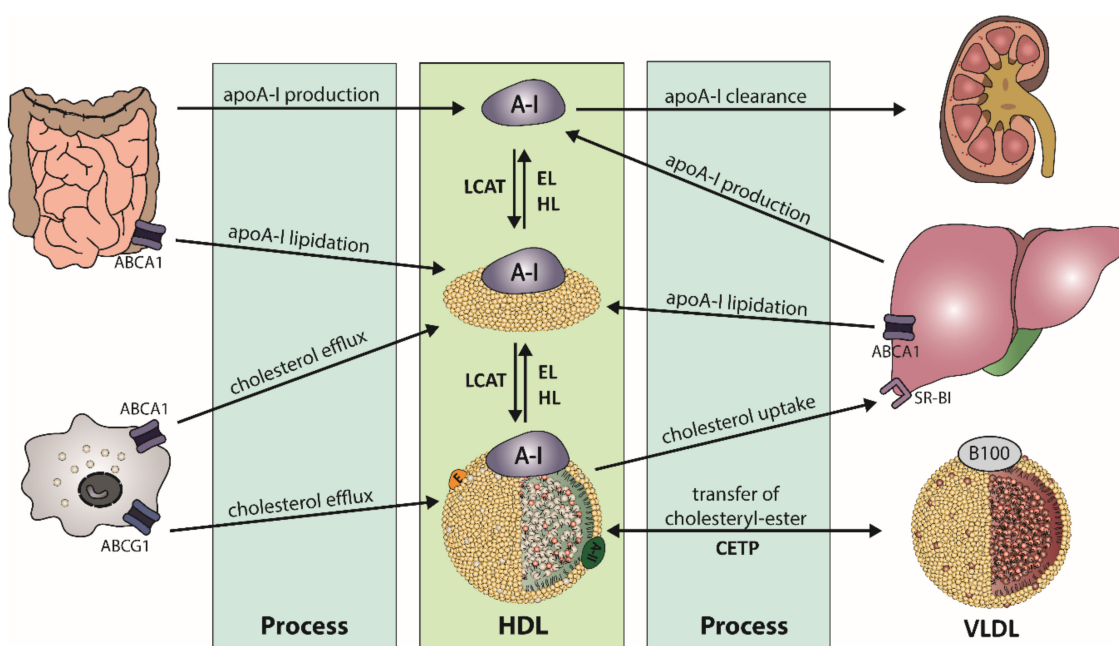
## 1. Introduction

The increasing prevalence of obesity in the last decades has become a major health problem worldwide. In Northern America and Europe, in particular, the number of overweight and obese people is ever increasing and is becoming more common in children and adolescents [1]. The causes of obesity are multifactorial, with the most important factors being excess calorie intake and lack of physical activity. Excessive body weight increases the risk of disease development, such as coronary artery disease, hypertension, type-2 diabetes mellitus, and dyslipidemia [2–6]. High levels of triglyceride-rich lipoproteins and low levels of high-density lipoprotein cholesterol (HDL-C) commonly characterize dyslipidemia in obesity. In obesity, not only HDL levels are altered, but an altered HDL distribution pattern and abnormal HDL metabolism have also been observed, which often leads to dysfunction of the HDL particles [7–9]. Consequently, the focus has shifted from studying the quantity of HDL to studying the quality of HDL [10]. The current review will focus on HDL metabolism and the pathophysiological changes seen in obesity. Further, we will focus on obesity-induced changes in HDL composition and the concomitant changes of HDL functionality. Another aspect will be the relationship of HDL with the adipokine adiponectin as well as with the bioactive lipid sphingosine-1-phosphate (S1P), whose levels are altered in the state of obesity. We also summarize the effects of weight loss induced by bariatric surgery, Mediterranean diet and pharmacological approaches, which effectively increase HDL-C levels and improve HDL function.

## 2. HDL Metabolism, Structure, and Composition

### 2.1. HDL Metabolism

The biogenesis of HDL starts in the liver and the intestine, where apolipoprotein (apo) A-I is synthesized (Figure 1). After secretion, lipid-poor apoA-I interacts with the integral cell membrane protein ATP-binding cassette transporter A1 (ABCA1), which is abundantly expressed by hepatocytes and enterocytes [11]. Through interaction, apoA-I acquires lipids from the cellular lipid pool, generating nascent HDL particles. Additional lipids and apolipoproteins are acquired, which are derived from hydrolysis of triglyceride-rich lipoproteins. This process partly explains the strong inverse relationship of HDL-C and triglyceride levels, often observed in obese subjects [12]. The acquired cholesterol of HDL is further esterified by lecithin-cholesterol-acyl transferase (LCAT), forming mature HDL particles [13]. The reaction takes place at the surface of HDL and requires apoA-I as an activator for LCAT [14]. The generated HDL-associated cholesteryl-esters are partially transferred to apoB-containing lipoproteins by cholesteryl-ester transfer protein (CETP), usually in exchange for triglycerides. Another pathway for clearance of cholesteryl-ester in HDL is the direct uptake by the liver via scavenger receptor class B type 1 (SR-B1) [15]. After interaction of SR-B1 with large cholesterol-rich HDL, cholesteryl-esters and free cholesterol are internalized and cholesterol is removed through the bile, while apoA-I dissociates [16,17].



**Figure 1.** Schematic overview of high-density lipoprotein (HDL) metabolism. Biogenesis of apolipoprotein A-I (apoA-I) takes place in the liver and intestine. After secretion of the lipid-poor apoA-I, it interacts with ATP-binding cassette transporter A1 (ABCA1) to acquire lipids, leading to formation of nascent HDL. The enzyme lecithin-cholesterol-acyl transferase (LCAT) esterifies free cholesterol of nascent HDL to form mature HDL. Cholesteryl-esters are cleared by uptake of the liver by scavenger receptor B1 (SR-B1) or via transfer on triglyceride-rich lipoproteins by cholesteryl-ester transfer protein (CETP), in exchange of triglycerides. Triglyceride-rich HDL is susceptible to hydrolysis by endothelial lipase (EL) or hepatic lipase (HL).

HDL is enriched in triglycerides through the activity of CETP, generating HDL particles that are more susceptible to lipolysis by endothelial lipase (EL) or hepatic lipase (HL). Substrates for lipolysis are mainly phospholipids (EL) or phospholipids and triglycerides (HL), but with different specificity for phospholipids [18]. The lipolysis of triglycerides leads to the formation of smaller HDL particles, which are susceptible to faster catabolism. Another important key player of HDL metabolism is the

phospholipid transfer protein (PLTP), which transfers phospholipids between HDL particles and lipids between triglyceride-rich lipoproteins and HDL [19]. Many apolipoproteins, lipid transfer proteins, enzymes, cell surface receptors, and cellular lipid transporters are involved in the regulation of HDL metabolism and partly determine levels of plasma HDL-C. This complex metabolism produces HDL particles of varying size, density, and composition. Therefore, plasma HDL-C concentrations are not a good parameter to reflect functional properties of HDL, such as HDL-mediated reverse cholesterol transport or anti-oxidative or anti-inflammatory properties.

## 2.2. HDL Structure and Composition

Plasma levels of HDL-C have been associated with cardiovascular diseases for decades [20–22]. However, it is becoming widely accepted that it is not the quantity but the quality of HDL that is important, as HDL performs different functions depending on the protein and lipid composition [23–25]. ApoA-I is the most prevalent protein component of HDL, accounting for approximately 70% of the total protein [26]. ApoA-I has a variety of functions, such as activation of LCAT, interaction with cellular receptors, and anti-atherogenic activities [27–29]. ApoA-II is the second major apolipoprotein in HDL and presents about 15–20% of the total protein component [30]. The remaining 10–15% of HDL protein mass comprises minor proteins, including apoA-IV, ApoCs, which are important enzyme regulators, apoD, apoE, apoF, apoH, apoJ, ApoL-I, and apoM, and several enzymes. Paraonase 1 (PON1) is almost exclusively associated with HDL and has been shown to exert anti-inflammatory and anti-oxidative properties [31]. Other enzymes associated with HDL are LCAT and the platelet-activating factor acetyl hydrolase. The phospholipid transfer protein and CETP have a lipid transfer activity and are important in lipoprotein metabolism. Remarkably, it is not cholesterol that predominates the HDL lipidome, but phospholipids. Taken together, phospholipids and sphingolipids account for 40–60% of total lipids, while cholesteryl-ester (30–40%), triglycerides (5–12%), and free cholesterol (5–10%) are less abundant [23]. Similar to functions of HDL-associated proteins, HDL lipids also accomplish distinct structural functions. The lipid surface monolayer is constituted of phospholipids, while cholesteryl-ester and triglycerides form the hydrophobic core. In total, more than 200 lipids and 80 proteins are carried by different HDL subclasses, with individual HDL particles carrying only a few other proteins besides apoA-I [32–34].

## 2.3. HDL Subclasses

Multiple subclasses of HDL exist, depending on its stage of maturation, site of origin, and its protein and lipid composition. Thus, HDL particles are highly heterogeneous in their size, shape, structure, and density (Table 1). Pre- $\beta$  HDL is structurally the simplest form of HDL. These particles consist of one or two apoA-I molecules with a phospholipid layer and a trace amount of cholesterol. These particles are discoidal shaped with a diameter of approximately 9.6 nm and a thickness of 4.7 nm [35]. Pre- $\beta$  HDL particles rapidly take up cholesterol and phospholipids, which convert them into larger HDL subclasses. Therefore, pre- $\beta$  HDL only accounts for about 5% of HDL in the circulation [36]. Because of their function to avidly absorb cholesterol and phospholipids, pre- $\beta$  HDL particles are thought to be a major factor in preventing atherosclerotic plaque formation. Importantly, higher serum cholesterol efflux capacity is related to plasma concentrations of pre- $\beta$  HDL [37]. HDL3 particles have a smaller diameter (7.5 nm) and are enriched with proteins, while HDL2 particles are larger (10 nm) and lipid rich. Most abundant apolipoproteins are apoA-I and apoA-II in both subclasses; however, apoA-II is more present in HDL3. Interestingly, the HDL-associated enzyme PON1, which has anti-oxidative and anti-inflammatory properties [31], has been shown to be more frequently associated with HDL3. This higher abundance of PON1 on HDL3 could partly explain the higher anti-oxidative capacity of the smaller HDL particles [29,38]. HDL2 and HDL3 further show differences in lipid composition. Sphingolipids are, in general, less abundant in the HDL3 subclass, affecting surface lipid fluidity, whereas the bioactive lipid sphingosine-1-phosphate (S1P) is predominantly associated with HDL3 [23]. In line, the abundance of apoM, which specifically anchors S1P to HDL particle,

shows higher abundance in HDL3 [38]. S1P maintains vascular integrity and mediates multiple effects of HDL on endothelial cells [39]. The functions of HDL to induce vasorelaxation as well as promoting barrier function have been attributed to signaling of S1P [40,41]. Taken together, it seems that smaller subclasses of HDL have a greater protective potential than larger particles [29].

**Table 1.** Representation of HDL heterogeneity.

HDL Subclass	Size	Shape	Abundant Components	Important Functions
Pre- $\beta$ HDL	9.6 nm diameter, 4.7 nm thickness	discoidal	ApoA-I, phospholipids	ABCA1-Cholesterol efflux
HDL3	7.5 nm, 175 kDa	spherical	Protein:lipid ratio 55:45 PON1, ApoA-II, ApoM, S1P	Anti-oxidative activity Anti-inflammatory activity ABCA1-Cholesterol efflux
HDL2	10 nm, 350 kDa	spherical	Protein:lipid ratio 40:60	ABCG1- Cholesterol Efflux

Apo, apolipoprotein; ABCA1, ATP-binding cassette transporter A1; PON1, paraoxonase 1; ABCG1, ATP-binding cassette subfamily G member 1.

#### 2.4. Important Functions of HDL

One of the main functions of HDL is its ability to promote reverse cholesterol transport, the uptake of excess cholesterol from peripheral cells, and the transport to the liver for excretion. This process is considered as the major antiatherogenic effect of HDL [42].

The reverse cholesterol transport starts with the secretion of lipid-poor apoA-I, which is released from liver or intestine into the plasma to circulate to peripheral cells from which excess cholesterol is removed, forming nascent HDL. A key role in the reverse cholesterol transport is the interaction of apoA-I with ABCA1 [43]. Studies have shown that ABCA1 preferentially lipidates small HDL, specifically apoA-I, to form nascent HDL, while ATP-binding cassette subfamily G member 1 (ABCG1) stimulates cholesterol efflux to mature HDL and not to lipid-poor apoA-I [44,45]. Cholesterol efflux includes the passive diffusion of cholesterol from cells as well as the active cellular cholesterol transfer by ABCA1, ABCG1, and SR-BI [46–48]. The absorbed cholesterol is esterified by LCAT and mature HDL is formed. HDL-associated cholesteryl-ester is partially transferred to triglyceride-rich lipoproteins by CETP and further cleared by hepatic clearance through the low-density lipoprotein (LDL) receptor or taken up together with free cholesterol by the hepatic receptor SR-BI. Therefore, the transfer of cholesterol from peripheral cells to the liver involves two routes: (1) the direct uptake via SR-BI and (2) indirect by HDL-LDL/very low-density lipoprotein (VLDL) interaction [42]. In the liver, the cholesteryl-esters are hydrolyzed, and free cholesterol is either transported by ABCG5 and ABCG8 into the bile for excretion into feces or converted into bile acids or reused for VLDL production.

This process of HDL-mediated cholesterol efflux has been of expanded research interest in recent years. A number of different cell-based assays have been developed, to measure the ability of HDL to promote cholesterol efflux, the first step of reverse cholesterol transport. In the most established assay, a mouse macrophage cell line (J774) was employed [49]. Cells are enriched with radioactively or fluorescently labeled cholesterol and cyclic adenosine monophosphate to upregulate expression of ABCA1. For these assays, isolated HDL or apoB-depleted serum from patients is added to cell medium and the proportion between labeled cholesterol in the supernatant and in the cells is calculated.

Besides the ability of HDL to promote cholesterol efflux, there is increasing evidence that HDL-mediated antiatherogenic actions toward the endothelium have physiological relevance [50–53].

The beneficial properties of HDL on the endothelium include vasodilatory activity, primarily through stimulation of nitric oxide (NO) release from endothelial cells [40,54], and also the production of prostacyclin [55,56]. The initial step for the activation of NO production involves binding of HDL to SR-BI on the endothelium. Subsequent intracellular events are mediated by endothelial protein kinase B and intracellular  $Ca^{2+}$  mobilization, increase in intracellular ceramide levels, and the phosphorylation of the endothelial NO-synthase, leading to NO release [40,57–59]. HDL reduces the activity of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the endothelium, which reduces

the cellular production of superoxide, an inactivator of NO, thereby increasing NO bioavailability [60]. Vasodilatory actions of HDL further include cholesterol efflux of cholesterol and 7-oxysterols, mediated by ABCG1, which improves formation of active endothelial NO-synthase dimers, resulting in decreased production of reactive oxygen species [61].

Another anti-atherogenic function of HDL is its anti-oxidative activity by protecting LDL from oxidative damage induced by free radicals, thus reducing its atherogenicity. ApoA-I, the major protein component of HDL may play a central role in HDL-mediated anti-oxidative activity, by reduction of lipid hydroperoxides through methionine residues [62,63]. In addition, HDL-associated PON1 was shown to decrease lipid peroxidation of LDL and HDL through a specific cysteine residue [64]. Other apolipoprotein components and HDL-associated enzymes, such as apoA-II, apoE, apo, lipoprotein-associated phospholipase A2, and LCAT, may further contribute to the anti-oxidative properties [29,65,66]. HDL-associated lipophilic antioxidants such as tocopherols seem to make a small contribution to the antioxidant properties of HDL [67].

Additionally, to the number of anti-oxidative effects, HDL further possesses anti-inflammatory properties. In vitro experiments have shown that HDL inhibits transmigration of monocytes [68] and inhibits cytokine-induced expression of vascular cell adhesion molecule, intercellular cell adhesion molecule, and E-selectin expression [69,70]. By modulation of the nuclear factor  $\kappa$ B and the peroxisome proliferator-activated receptor gamma, HDL further inhibits the production of pro-inflammatory cytokines [71]. Due to these capabilities, HDL reduces the recruitment of lymphocytes, monocytes, and basophils to the vascular endothelium, thereby decelerating downstream events of inflammatory response.

### 3. HDL-C-Raising Therapies and Cardiovascular Outcome

The cholesterol component of HDL has been shown to be inversely associated with the risk of coronary heart disease (CHD) and is a key component of predicting cardiovascular risk in the general population [12]. The Framingham Heart Study was the first study to observe the strong association between HDL-C and CHD and, therefore, served as the basis for the hypothesis that HDL, as the “good” cholesterol, might hold protective properties against CHD [72]. However, more recent data clearly indicate that the association between HDL-C concentration and all-cause mortality is U-shaped, and both extremely high and low HDL-C concentrations are associated with an increase in mortality [73]. This leads to considerable uncertainty about the potential benefit of increasing HDL-C and may reflect or explain the disappointing results of recent clinical studies on a number of therapeutic interventions aimed at increasing HDL-C levels, such as CETP inhibitors [74–76]. Given the heterogeneity of HDL particles in terms of structure, size, lipidomic/proteomic composition, and metabolism, HDL-C values are only a snapshot of the steady-state cholesterol pool. HDL-C values provide no direct information on the rate of cholesterol efflux from vascular macrophages in liver, which is influenced by many factors beyond the mass of HDL-C alone. Furthermore, the circulating HDL-C concentrations do not provide information about the anti-inflammatory, anti-oxidant, anti-thrombotic, and endothelial function-promoting activities of HDL [77]. Therefore, considerable interest has recently focused on approaches to influence the biological functions of HDL in the search for new cardioprotective therapies [78–84]. This is based on new findings that underline the importance of HDL functionality [85–87], which has led to ongoing efforts to develop new risk markers and therapeutics that focus on HDL quality rather than quantity.

### 4. Obesity Alters HDL-C Levels

Obesity is commonly accompanied by low HDL-C levels and an increase in triglyceride-rich lipoproteins [88], which is often termed as atherogenic dyslipidemia. Characteristic for this dyslipidemia is a decreased clearance of triglyceride-rich lipoproteins, which is caused by a relative lack of insulin-sensitive lipoprotein lipase [89–91]. Lipoprotein lipase hydrolyzes triglycerides of chylomicrons and VLDL, leading to shrinkage of the particles and transfer of surface phospholipids and





Another characteristic of obesity is an imbalance of adipokines, including leptin. Leptin is mainly produced by adipocytes and is elevated in overweight and obese individuals [100,101]. Interestingly, a study in children showed that plasma leptin levels correlated with HDL-C [102]. Further, a correlation between leptin and HDL-associated triglycerides and with HDL particle size has been reported in adults [103]. In vivo experiments in leptin-deficient (ob/ob) mice suggest that leptin upregulates hepatic SR-BI and thereby influences levels of HDL-C [104].

In the state of obesity, increased CETP levels are correlated with leptin levels [105], in line with the fact that adipose tissue is one of the major sources of CETP expression [106]. Therefore, the obesity-associated increase in CETP production is thought to affect HDL-C levels [107].

Another molecule, secreted from adipose tissue, which may have a direct impact on HDL metabolism, is the adipokine adiponectin. Studies have shown that levels of adiponectin, which are reduced in the state of obesity, are directly correlated with plasma HDL-C levels [108–112]. Furthermore, an intervention study showed that levels of adiponectin as well as of HDL-C are increasing after weight loss and that this improvement was independent of changes in insulin sensitivity and fat mass [113]. The relationship of HDL with adiponectin will be discussed in Section 5.3 in more detail.

As mentioned above, the activity of hepatic lipase is increased in obesity and insulin resistance [96–98,114,115], leading to faster clearance of triglyceride-rich HDL [116], which is produced by CETP-mediated transfer. The triglyceride-enriched HDL is a more susceptible substrate for hepatic lipase and, therefore, undergoes rapid hydrolysis [99,117]. The mechanisms underlying the increase in hepatic lipase activity in obese states are not yet understood, but it appears that hepatic insulin resistance plays an important role [118]. However, further studies are needed to clarify the link between HDL metabolism and hepatic lipase expression in obesity and insulin resistance.

Another lipase, which may affect HDL-C levels in obesity or insulin resistance is endothelial lipase. Experiments with rodents already revealed the impact of endothelial lipase on HDL metabolism: Inhibition or genetic deletion of endothelial lipase resulted in elevated levels of HDL-C by reduction of catabolism rate [119–121], while overexpression of endothelial lipase caused a reduction of HDL-C by increased catabolism rate [119,122,123]. Human studies further have shown that some rare genetic variants in the endothelial lipase gene are linked with high HDL-C levels and that they are correlated to levels of plasma endothelial lipase mass [124,125]. In obesity, levels of endothelial lipase have been shown to be significantly elevated, proposing an upregulation of endothelial lipase during obese states, which may contribute to the reduced HDL-C levels [124]. Obesity is characterized by low-grade inflammation, leading to infiltration of immune cells into adipose tissue [126,127]. The obesity-induced inflammation may decrease HDL-C levels by upregulation of endothelial lipase. However, the significance of endothelial lipase on low levels of HDL-C in the obese state further needs to be investigated.

Another factor affecting HDL-C is cholesterol released by adipocytes. In humans, adipose tissue is a major site for cholesterol storage and contains up to 25% of total body cholesterol in normal-weight subjects and approximately half of it in obese states [128,129]. In adipose tissue, nearly all of the cholesterol is stored in the unesterified form, as free cholesterol, which makes adipocytes unique among cells [129–132]. It is well reported that adipocytes express the major cholesterol transporters ABCA1 and SR-BI as well as ABCG1, but in a much lesser extent [133]. Adipocytes are promoting cholesterol transfer to HDL via ABCA1 and SR-BI, representing a direct factor for modulation of HDL-C levels. Importantly, Zhang et al. demonstrated that lack of adipose ABCA1 resulted in reduced levels of HDL-C and caused a backlog of cholesterol within adipose tissue [134]. Further, they showed that adipocyte inflammation, which is a hallmark of central obesity, downregulates ABCA1 and SR-BI expression and impairs cholesterol efflux from adipocytes to HDL. Therefore, their results suggest a direct impact of adipose tissue on modulation of HDL-C and that obesity-induced inflammation of adipocytes may result in impaired cholesterol efflux to HDL, contributing to reduced HDL-C levels.

Concluding, several factors and mechanisms are involved in the reduction of HDL-C levels in the obese state, but further research on these mechanisms is of importance to find novel treatment strategies improving HDL quality and quantity.

## 5. Obesity, HDL, and Cardiovascular Risk

Obesity is one of the major risk factors for cardiovascular disease, which is associated with atherogenic dyslipidemia. These alterations in plasma lipid and lipoprotein levels contribute to the manifestation of such a severe morbidity.

### 5.1. Obesity Leads to a Shift in HDL Subclass Distribution

As described above, plasma HDL-C levels do not adequately reflect protective functions of HDL and greater protective potential is attributed to the smaller, more dense HDL particles. Recent studies of Woudberg et al. assessed HDL subclass distribution in normal-weight and obese white and black South African women. In obese study participants, a shift from large HDL toward increased levels of intermediate and small HDL subclasses was seen, whereby the effect was more pronounced in white women [135]. In a 5.5-year follow-up study they showed that the shifts in HDL subclass distribution were related to increasing central adiposity, suggesting a link between body fat distribution and lipid metabolism [8]. Based on the observed changes in HDL subclass distribution in obese individuals, Woudberg et al. explored the effect of exercise training on HDL subfractions. Interestingly, 12 weeks of exercise intervention altered the distribution of small HDL in obese women [136].

In adolescents suffering from type 2 diabetes mellitus, Davidson et al. determined the risk factors associated with the depletion of large HDL particles and simultaneous accumulation of small particles [137]. The authors investigated the distribution of HDL subclasses of individuals who differed in body mass index and insulin sensitivity and found that obesity is the major risk factor linked to the altered HDL subclasses. An increased CETP-mediated transfer of triglycerides on HDL and the subsequent hydrolysis of triglyceride-enriched HDL by hepatic lipase appeared to be the mechanism underlying the shift of large HDL to small and dense HDL particles [137].

### 5.2. Obesity Affects HDL Function

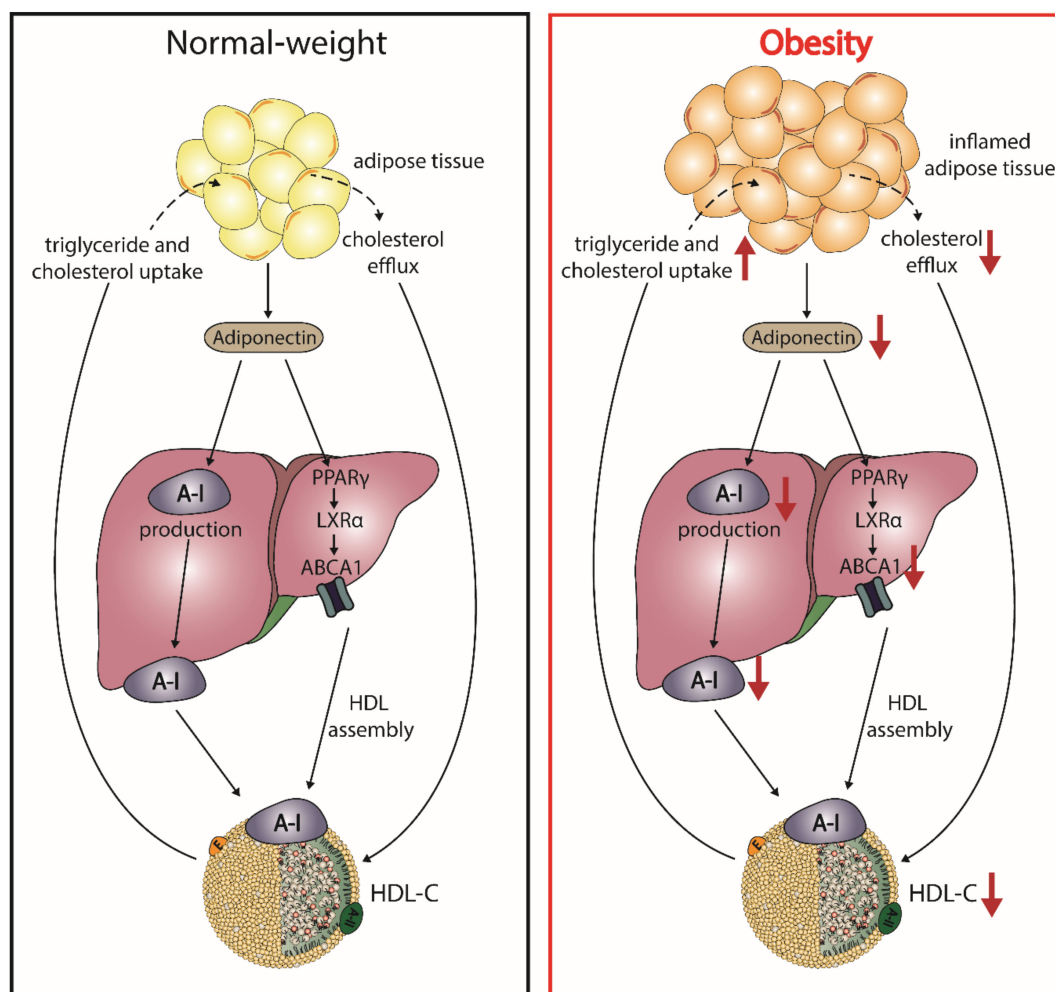
It is known that HDL functionality is severely impaired in certain diseases and HDL may even have inflammatory or pro-atherogenic properties. This was clearly demonstrated in HDL from patients suffering from chronic kidney disease [138,139], diabetes [140], cardiovascular disease [86], liver disease [141], psoriasis [142], or even atopic dermatitis [143] and allergic rhinitis [144]. Obesity-associated complications, such as inflammation or diabetes, have been shown to render HDL dysfunctional. HDL isolated from type 2 diabetes patients did not reduce endothelial oxidant stress and did not improve endothelium-dependent vasodilatation when compared to HDL isolated from healthy subjects [145]. Vasodilatory activity of HDL has been shown to be inversely correlated with triglyceride content of HDL, which is elevated in obesity [146]. A reduction of the overall capacity of HDL to promote cholesterol efflux from fibroblasts in obese, compared to lean, normal-weight, subjects was reported [147]. Of particular interest, cholesterol efflux capacity appears to be significantly inversely correlated with the body mass index [148,149]. Since cholesterol efflux capacity is the main metric of HDL function and has strong inverse association with coronary artery disease [85,150,151], the reduction of efflux capacity in obesity may have a crucial impact on the development of cardiovascular disease.

### 5.3. Adiponectin and HDL

It has been well reported that plasma HDL-C concentrations show a strong correlation with levels of adiponectin, independent of body mass index, distribution of body fat, and insulin sensitivity [108–112]. Adiponectin is mainly secreted by adipocytes, shows anti-atherogenic properties, and modulates glucose metabolism [152,153]. Studies with mice overexpressing or lacking adiponectin as well as in vitro studies suggest a causal relationship with HDL-C levels.



Adiponectin increases the production of apoA-I as well as hepatic ABCA1, which increases HDL-C levels (Figure 3) [154,155]. The enhanced expression of ABCA1 has been suggested by activation of liver X receptor alpha and peroxisome proliferator-activated receptor gamma [156–158]. Plasma levels of adiponectin show a negative correlation with fractional catabolic rate of apoA-I in individuals with metabolic syndrome and control subjects [159]. Besides ABCA1, adiponectin upregulates ABCG1 expression, increases cholesterol efflux capacity, and efficiently promotes lipidation of apoA-I, leading to formation of nascent HDL [160].



**Figure 3.** Postulated effects of obesity on adiponectin and HDL metabolism. In normal-weight subjects, adipocytes produce adiponectin, which enhances expression of the ATP-binding cassette transporter A1 (ABCA1) through activation of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) and liver X receptor alpha (LXR $\alpha$ ), leading to HDL assembly. Further, adiponectin increases the hepatic production of apoA-I. During the state of obesity, adipocytes manifest several altered properties, which play a role in the reduction of HDL-C. Increased inflammation and fat accumulation in the adipocytes reduces the production of adiponectin and impairs cholesterol flux to HDL. The reduction of adiponectin downregulates apoA-I production and ABCA1 expression in hepatocytes, thus reducing HDL assembly.

Adiponectin has been consistently reported to be associated with cholesterol efflux capacity of HDL [148,161,162]. Other studies have shown an inverse association of hepatic lipase with serum adiponectin levels [163,164]. Adiponectin might inhibit the hepatic lipase-mediated hydrolysis of triglycerides and phospholipids of HDL2 particles. This is in line with studies showing an association of adiponectin with HDL particle size and HDL2 [165–168]. However, further studies are needed to prove causality. Another further mechanism suggested that adiponectin increases lipoprotein

lipase activity, thereby accelerating clearance of triglyceride-rich particles. This, in turn, would lead to less exchange of triglycerides and cholesteryl-ester by CETP and, thus, to cholesteryl-ester-enriched HDL2 particles. A positive correlation between circulating adiponectin and post-heparin lipoprotein lipase activity has been reported [169,170], but causality has to be proven to draw firm conclusions. Low-grade inflammation and fat accumulation cause a dysregulated adipokine production [171,172] and markedly reduce adiponectin levels [173,174]. Therefore, low adiponectin observed in obesity levels may explain, at least in part, the shift of large HDL to small HDL particles.

#### 5.4. Obesity and HDL-Associated Sphingosine-1-Phosphate (S1P)

Of particular importance, the complete sphingolipid metabolism is altered in obesity [175]. In obese individuals the levels of ceramides, sphingosine, sphinganine, and S1P are increased in adipocytes when compared to lean controls [175]. The bioactive lipid S1P is mainly carried via apoM anchored to HDL (about 65%) and to a lesser extent via albumin (about 25%) or LDL/VLDL (about 10%) [39]. The half-life of S1P is prolonged when it is associated with HDL, when compared with albumin-associated S1P [176]. S1P is a member of the sphingolipid family, a large group of molecules with a wide range of physiological functions. S1P in the circulation is mainly derived from erythrocytes, vascular endothelial cells, and platelets [177,178]. S1P activates five different G protein-coupled receptors, termed S1P receptors 1–5 (S1PR1–5), in an autocrine or paracrine manner [179].

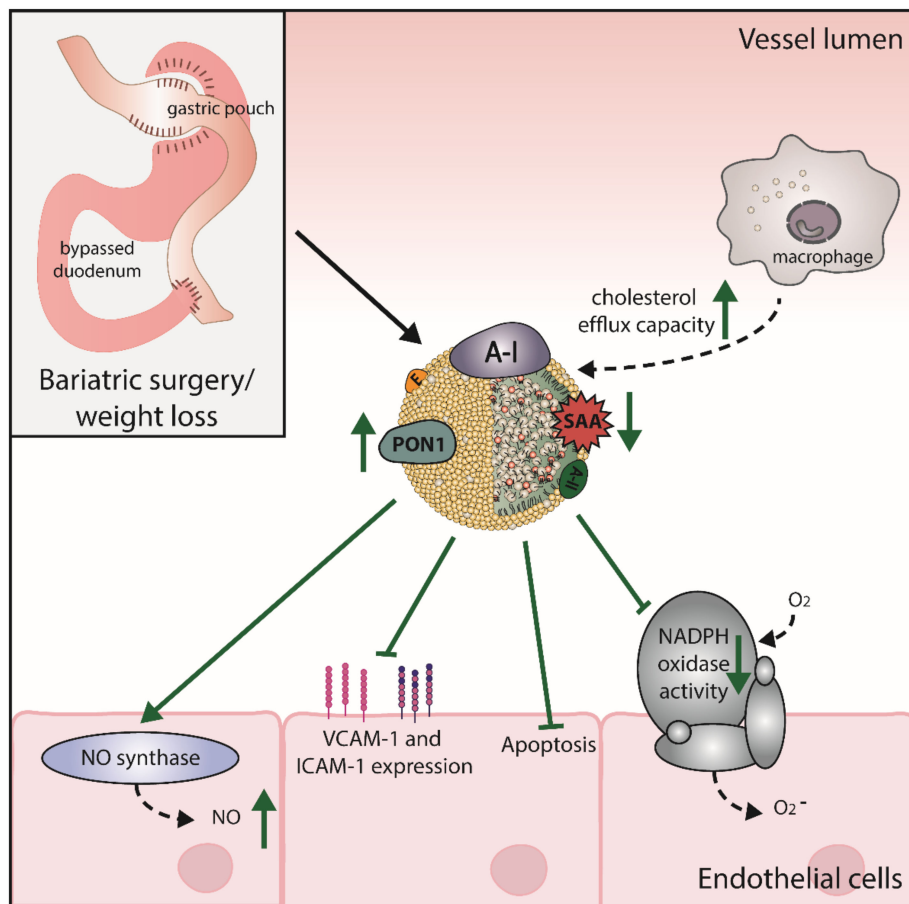
Kowalski et al. observed that levels of S1P are elevated in plasma of obese humans and rodents and that the levels correlate with metabolic abnormalities such as adiposity and markers of insulin resistance [180]. However, this increase of S1P could not be confirmed in a study comparing levels between overweight and lean adolescents [181]. More recently, the group of Green et al. analyzed the liver metabolome of mice after caloric restriction and revealed that caloric restriction had an impact on S1P signaling [182]. The authors observed that as a response to caloric restriction, liver expression of S1P was significantly increased. S1P levels were negatively associated with decreasing body mass, leptin, and insulin-like growth factor-1. Another study investigated the role of S1P/S1PR1 signaling in the regulation of energy homeostasis in rodents [183]. The authors showed that S1PR is highly expressed in the hypothalamus and that a fasting period of 12 h could reduce S1PR level, whereas refeeding restored the protein levels of the receptor in the hypothalamus. Altogether, their results indicated that the S1P/S1PR1 axis plays a critical role in energy balance and represents a potential target for treatment of obesity. The potential role of S1P signaling in energy metabolism was strengthened by Christoffersen et al., showing that lack of apoM in mice increases the amount of brown adipose tissue and that the turnover of fat is increased, resulting in low white adipose tissue mass and low body weight [184]. These effects of apoM knockout suggest that pharmacological modulation of S1PRs may be a promising approach for the treatment of obesity and associated diseases in the future [185].

Noteworthy, only a small number of studies investigated plasma levels of S1P in obese or overweight human subjects. While obesity is associated with a shift from large HDL to small and dense HDL, S1P has to be increasingly transported with alternative chaperones, reducing the effectiveness of S1P [8]. In line with this hypothesis, Frej et al. showed that a shift in apoM/S1P between HDL particles in women was associated with impaired anti-inflammatory effects of the apoM/S1P complex [186].

## 6. Bariatric Surgery Improves HDL Levels and Function

Bariatric surgery has been demonstrated as the most effective intervention for patients with severe obesity, which induces sustained long-term weight reduction associated with decreased obesity-associated comorbidities and cardiovascular mortality [187–190]. The standard bariatric surgeries are Roux-en-Y gastric bypass (RYGB), where most of the stomach is bypassed, creating a small gastric pouch; whereas sleeve gastrectomy resects the gastric fundus and most of the gastric body [191]. RYGB surgeries resulted in significant improvements of plasma lipid levels, decreased risk of cardiovascular disease, and overall mortality [192–195]. Further, after RYGB, levels of circulating adiponectin increased, insulin sensitivity improved, and blood pressure levels were reduced [196–198].

Of particular interest is that the plasma levels of HDL-C after bariatric surgery were remarkably improved compared to the preoperative values and compared to people who only received medical therapy for weight loss [195,199–202]. In the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) clinical trial, obese patients with type 2 diabetes mellitus were randomly assigned to receive intensive medical therapy alone or in combination with RYGB or sleeve gastrectomy. Five years after surgical procedures, the levels of HDL-C were increased by 32%, 30%, and 7% in the RYGB, sleeve gastrectomy, and medical therapy alone groups, respectively [201]. In a substudy, Lorkowski et al. investigated serum HDL function, by determining the apoA-I exchange rate and cholesterol efflux capacity in the STAMPEDE study. The apoA-I exchange rate is determined by adding labeled apoA-I to serum samples and recording labeled apoA-I incorporation into serum HDL [203]. This apoA-I exchange rate has been linked with risk of major adverse cardiovascular events [203]. HDL in both RYGB and sleeve gastrectomy groups showed improved functionality, by increased apoA-I exchange rate after one and five years compared to baseline. Moreover, also cholesterol efflux capacity after five years was improved when compared to pre-operative samples (Figure 4). Improvement of cholesterol efflux capacity appears to depend on the procedure, with an improvement only with sleeve gastrectomy, but not with RYGB at six months after surgery [204]. However, after 12 months both operations resulted in improved cholesterol efflux capacity [204].



**Figure 4.** Proposed effects of bariatric surgery on metrics of HDL function. After surgical procedure, HDL shows increased cholesterol efflux capacity, improved paraoxonase 1 (PON1), and reduced levels of serum amyloid A (SAA). Further, HDL of patients after bariatric surgery inhibits expression of the vascular adhesion molecule (VCAM-1) and intracellular adhesion molecule (ICAM-1), improves endothelial anti-apoptotic properties, and reduces nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity. Bariatric surgery also improved HDL-mediated production of nitric oxide (NO) and, thus, improved endothelial function.

In addition, other metrics of HDL function were assessed in morbidly obese patients after bariatric procedure. Six months after surgery, the antioxidant potential of HDL was increased, accompanied by an increase in PON1 protein levels. Further, alterations in the distribution of HDL subpopulations with a shift toward more mature HDL as well as an increase in apoA-I/apoE ratio was found [205].

Laparoscopic adjustable gastric banding is another type of weight-loss surgery, which is minimally invasive and associated with low rates of associated complications and mortality rates [206]. Recently, the impact of laparoscopic adjustable gastric banding on HDL subclass distribution was studied [207]. The authors observed an increase in large HDL and intermediate HDL subclasses and a decrease of the small HDL subfraction [207]. Similar to this, another study observed an increase in the large HDL subfractions after laparoscopic adjustable gastric banding and a reduction of HDL-associated pro-inflammatory serum amyloid A [208].

Another study evaluated whether RYGB restores protective properties of HDL and reverses the obesity-induced endothelial dysfunction [209]. In a rat model of RYGB as well as in human samples, endothelium protective activities of HDL were improved and associated with increased plasma levels of the gut hormone glucagon-like peptide-1 and bile acids. HDL isolated from patients after RYGB led to restored endothelial nitric oxide synthase, increased nitric oxide release and, in parallel, a reduction of endothelial nicotinamide adenine dinucleotide phosphate oxidase, and decrease in endothelial apoptosis and vascular adhesion molecule expression. Moreover, the ability of HDL to induce cholesterol efflux from macrophages as well as PON1 activity was enhanced. Interestingly, 12 weeks after RYGB, the properties of HDL were improved to levels of healthy subjects, although the patients were still obese [209]. A recently published study confirmed the improvement of cholesterol efflux capacity and PON1 activity 12 months after RYGB and observed an association of miR-222 and miR-223, both reported to play an important role in the pathophysiology of obesity [210,211], with markers of HDL function [212].

Altogether, the current state of research suggests that the marked increase in HDL quality and quantity observed after bariatric surgery is likely linked to reduction of obesity-related comorbidities and cardiovascular mortality.

## 7. Effects of Pharmacological Anti-Obesity Interventions on HDL Levels and Function

Changes in dietary and physical lifestyle have been shown to result in a limited reduction in bodyweight (3–10%) and that most people regained weight again [213]. Therefore, besides bariatric surgery, complementary treatments with anti-obesity drugs are a strategy to achieve permanent weight loss in pathologically obese individuals. In 1959, the first anti-obesity drug, termed phentermine was approved by the United States Food and Drug Administration. Nowadays, a number of pharmacotherapies have become available to treat obesity.

Phentermine belongs to the group of sympathomimetics and is the most commonly prescribed anti-obesity drug in the USA [214]. Twelve weeks of administration of phentermine reduced body weight and decreased levels of total cholesterol in Korean obese subjects [215].

A combination therapy of phentermine with topiramate has been shown to induce greater weight loss than either drug alone and showed fewer occurrence of side effects [216]. Administration of phentermine and topiramate in overweight and obese patients with dyslipidemia showed improvements in HDL-C levels and non-HDL-C levels vs. the placebo group at week 56 [217]. Another study designed to evaluate the long-term efficacy of phentermine/topiramate treatment found that the HDL-C levels of study participants increased more than in the placebo group [218].

Orlistat is an intestinal lipase inhibitor that prevents breakdown of triglycerides and has an excellent long-term safety record [216]. Interestingly, orlistat causes a 25% reduction in cholesterol absorption [219]. Regarding orlistat-induced changes in HDL-C levels, studies are inconsistent. Some studies reported a significant increase of HDL-C in patients receiving orlistat [200–222], while others observed no significant changes [223–225].

Noteworthy, food intake only minimally affects HDL-C [226,227], which might explain the inconsistent effects of orlistat on HDL-C levels.

Lorcaserin is a serotonin 2c receptor agonist available in the USA that increases central serotonin release and has been shown to be effective for long-term weight management [228,229]. A recent study showed that lorcaserin treatment for six months resulted in decrease of LDL-C, while plasma levels of HDL-C were increased [230]. Lipid subfraction analysis further revealed an increase in HDL particle size.

Liraglutide is a glucagon-like peptide-1 receptor agonist widely used to treat type 2 diabetes. This drug further increases satiety, slows gastric emptying, and also decreases body weight, besides reducing glucose concentration [231]. Long-term treatments with liraglutide have been shown to reduce body weight and waist circumference, but also to improve plasma lipid levels, including an increase in HDL-C levels [232,233].

Overall, most pharmacological approaches for obesity treatment increase HDL-C. Further studies examining potential effects of anti-obesity treatment on metrics of HDL function are warranted.

## 8. Effects of Dietary Approaches on HDL Levels and Function

Other strategies to treat obesity, besides pharmacological treatments and surgical procedures, are hypocaloric diets, such as intermittent fasting and caloric restriction. Furthermore, dietary patterns including Mediterranean diet are commonly used to induce weight loss and improve cardiovascular health in obese individuals [234,235].

Caloric restriction is the most common form of dietary restriction, in which subjects strive to decrease their daily energy intake by 15–40% of baseline needs each day [236]. In a 16-week intervention trial in which obese diabetic participants were given a very low calorie diet (450 kcal/day), caloric restriction was shown to reduce CETP activity and increase ApoA-I levels, but did not affect HDL-C levels or HDL cholesterol efflux capacity [237]. Another recently published study compared the effect of an 8-week intermittent caloric restriction regimen to continuous caloric restriction in overweight and obese subjects. They observed that these interventions similarly reduced body weight and fat mass and improved plasma triglycerides but had no effect on levels of HDL-C [238]. Interestingly, Liang et al. observed that a 3-month intervention of caloric restriction, together with moderate physical activity, resulted in weight reduction in obese subjects with metabolic syndrome but decreased PON1 levels [239]. In line with this, another study with obese participants observed that a low-calorie diet reduced PON1 enzyme activity [240]. Furthermore, weight loss through caloric restriction has been shown to decrease LCAT activity in obese [241] as well as in normal-weight subjects [242].

Alternate-day fasting (ADF) regimens consist of a “feeding day”, with ad libitum feeding and a “fasting day”, with complete abstinence of food and drink intake, except for water for 24 h. These regimens are less common than caloric restriction but were created to facilitate compliance with dietary restriction protocol, as these regimens require energy restriction only every-other day. In a modified ADF study, in which obese participants were allowed to consume 25% of their regular energy needs on the fasting day, body weight and body fat decreased and also levels of triglycerides, total cholesterol, and LDL-C decreased, whereas levels of HDL-C remained unchanged [243]. Varady et al. demonstrated that the same ADF regimen was effective in both weight reduction and cardioprotection in normal-weight and overweight subjects [244]. After 12 weeks of ADF, the study participants showed decreased body weight and fat mass, but no changes in the levels of HDL-C were observed. Similar results were observed in another ADF intervention study in normal-weight participants [245].

Mediterranean diet is a dietary approach to induce weight loss and to prevent cardiovascular events [234]. This diet pattern is generally characterized by high consumption of vegetables, fruits, nuts, legumes, wheat-based cereals, olive oil, and fish; moderate consumption of dairy products and poultry; and low consumption of red and processed meats [246]. In the Prevention with Mediterranean Diet study (PREDIMED), individuals with high cardiovascular risk were assigned to a Mediterranean



diet supplemented with extra-virgin olive oil or nuts and had lower incidence of cardiovascular events than the control group, assigned to a reduced-fat diet [247]. A substudy, including volunteers of the PREDIMED trial, concentrated on examining the effect of this anti-oxidant-rich dietary pattern on HDL function. Of particular interest, they observed that a 1-year Mediterranean diet, enriched with olive oil or nuts, increased the HDL cholesterol efflux capacity, PON1 activity, and HDL vasodilatory activity [248]. Similarly, another study showed that 12 weeks of Mediterranean diet and exercise improved HDL cholesterol efflux capacity and improved HDL function by inhibiting myeloperoxidase-mediated oxidative stress in subjects with metabolic syndrome [249].

## 9. Conclusions

Obesity leads to a depletion of HDL-C, due to a marked shift from large cholesteryl-ester-rich HDL to small and dense triglyceride-rich particles. The mechanisms underlying this shift are multifactorial, including elevated CETP activity linked to increased levels of triglyceride-rich lipoproteins, lower adiponectin levels, and increased clearance of large HDL particles. These changes in HDL subspecies are accompanied by changes in composition and functionality. S1P will potentially be attached to alternative chaperones, resulting in attenuated multiple beneficial effects of S1P. Bariatric surgery is currently the most effective treatment for raising HDL-C levels and, more importantly, it also significantly improves HDL functionality and may be related, at least in part, to the reduction in mortality observed in observational studies. In addition, there is accumulating evidence that Mediterranean diet, especially when enriched with virgin olive oil, significantly enhances parameters of HDL atheroprotective functions. Further studies are warranted to identify specific components in olive oil or other nutrients that improve HDL function. Most pharmacological approaches for obesity treatment increase HDL-C but further studies examining potential effects of anti-obesity treatment on metrics of HDL function are needed. The data of caloric restriction strategies are inconsistent and even show negative effects on some metrics of HDL functionality.

Considerable interest has recently focused on approaches to influence the biological functions of HDL in the search for new cardioprotective therapies and might establish novel treatment strategies in obese individuals.

**Funding:** This work was supported by the Austrian Science Fund (FWF) (DOC 31-B26) and the Medical University Graz through the PhD Program Inflammatory Disorders in Pregnancy (DP-iDP).

**Acknowledgments:** Open Access Funding by the Austrian Science Fund (FWF).

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Knight, J.A. Diseases and Disorders Associated with Excess Body Weight. *Ann. Clin. Lab. Sci.* **2011**, *41*, 107–121. [[PubMed](#)]
2. Poirier, P.; Giles, T.D.; Bray, G.A.; Hong, Y.; Stern, J.S.; Pi-Sunyer, F.X.; Eckel, R.H. Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 968–976. [[CrossRef](#)] [[PubMed](#)]
3. Zeller, M.; Steg, P.G.; Ravisy, J.; Lorgis, L.; Laurent, Y.; Sicard, P.; Janin-Manificat, L.; Beer, J.C.; Makki, H.; Lagrost, A.C.; et al. Relation Between Body Mass Index, Waist Circumference, and Death After Acute Myocardial Infarction. *Circulation* **2008**, *118*, 482–490. [[CrossRef](#)] [[PubMed](#)]
4. Al-Goblan, A.S.; Al-Alfi, M.A.; Khan, M.Z. Mechanism linking diabetes mellitus and obesity. *Diabetes Metab. Syndr. Obes. Targets Ther.* **2014**, *7*, 587–591. [[CrossRef](#)]
5. Narkiewicz, K. Obesity and hypertension—The issue is more complex than we thought. *Nephrol. Dial. Transplant.* **2006**, *21*, 264–267. [[CrossRef](#)]
6. Bays, H.E.; Toth, P.P.; Kris-Etherton, P.M.; Abate, N.; Aronne, L.J.; Brown, W.V.; Gonzalez-Campoy, J.M.; Jones, S.R.; Kumar, R.; La Forge, R.; et al. Obesity, adiposity, and dyslipidemia: A consensus statement from the National Lipid Association. *J. Clin. Lipidol.* **2013**, *7*, 304–383. [[CrossRef](#)]

7. Rashid, S.; Genest, J. Effect of obesity on high-density lipoprotein metabolism. *Obesity* **2007**, *15*, 2875–2888. [CrossRef]
8. Woudberg, N.J.; Lecour, S.; Goedecke, J.H. HDL Subclass Distribution Shifts with Increasing Central Adiposity. Available online: <https://www.hindawi.com/journals/job/2019/2107178/> (accessed on 10 August 2020).
9. Wang, H.; Peng, D.-Q. New insights into the mechanism of low high-density lipoprotein cholesterol in obesity. *Lipids Health Dis.* **2011**, *10*, 176. [CrossRef]
10. Rader, D.J.; Tall, A.R. Is it time to revise the HDL cholesterol hypothesis? *Nat. Med.* **2012**, *18*, 1344–1346. [CrossRef]
11. Parks, J.S.; Chung, S.; Shelness, G.S. Hepatic ABC transporters and triglyceride metabolism. *Curr. Opin. Lipidol.* **2012**, *23*, 196–200. [CrossRef]
12. Rader, D.J.; Hovingh, G.K. HDL and cardiovascular disease. *Lancet* **2014**, *384*, 618–625. [CrossRef]
13. Norum, K.R.; Remaley, A.T.; Miettinen, H.E.; Strøm, E.H.; Balbo, B.E.P.; Sampaio, C.A.T.L.; Wiig, I.; Kuivenhoven, J.A.; Calabresi, L.; Tesmer, J.J.; et al. Lecithin:cholesterol acyltransferase: Symposium on 50 years of biomedical research from its discovery to latest findings. *J. Lipid Res.* **2020**, *61*, 1142–1149. [CrossRef] [PubMed]
14. Sorci-Thomas, M.G.; Bhat, S.; Thomas, M.J. Activation of lecithin: Cholesterol acyltransferase by HDL ApoA-I central helices. *Clin. Lipidol.* **2009**, *4*, 113–124. [CrossRef] [PubMed]
15. Acton, S.; Rigotti, A.; Landschulz, K.T.; Xu, S.; Hobbs, H.H.; Krieger, M. Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. *Science* **1996**, *271*, 518–520. [CrossRef]
16. Schaefer, E.J.; Anthanont, P.; Asztalos, B.F. HDL metabolism, composition, function and deficiency. *Curr. Opin. Lipidol.* **2014**, *25*, 194–199. [CrossRef]
17. Kozarsky, K.F.; Donahue, M.H.; Rigotti, A.; Iqbal, S.N.; Edelman, E.R.; Krieger, M. Overexpression of the HDL receptor SR-BI alters plasma HDL and bile cholesterol levels. *Nature* **1997**, *387*, 414–417. [CrossRef]
18. Duong, M.; Psaltis, M.; Rader, D.J.; Marchadier, D.; Barter, P.J.; Rye, K.-A. Evidence that hepatic lipase and endothelial lipase have different substrate specificities for high-density lipoprotein phospholipids. *Biochemistry* **2003**, *42*, 13778–13785. [CrossRef]
19. Albers, J.J.; Vuletic, S.; Cheung, M.C. Role of Plasma Phospholipid Transfer Protein in Lipid and Lipoprotein Metabolism. *Biochim. Biophys. Acta* **2012**, *1821*, 345–357. [CrossRef]
20. Voight, B.F.; Peloso, G.M.; Orho-Melander, M.; Frikke-Schmidt, R.; Barbalic, M.; Jensen, M.K.; Hindy, G.; Hólm, H.; Ding, E.L.; Johnson, T.; et al. Plasma HDL cholesterol and risk of myocardial infarction: A mendelian randomisation study. *Lancet* **2012**, *380*, 572–580. [CrossRef]
21. Toth, P.P.; Barter, P.J.; Rosenson, R.S.; Boden, W.E.; Chapman, M.J.; Cuchel, M.; D’Agostino, R.B.; Davidson, M.H.; Davidson, W.S.; Heinecke, J.W.; et al. High-density lipoproteins: A consensus statement from the National Lipid Association. *J. Clin. Lipidol.* **2013**, *7*, 484–525. [CrossRef]
22. Kannel, W.B.; Dawber, T.R.; Friedman, G.D.; Glennon, W.E.; Mcnamara, P.M. Risk Factors in coronary heart disease. An evaluation of several serum lipids as predictors of coronary heart disease; The Framingham Study. *Ann. Intern. Med.* **1964**, *61*, 888–899. [CrossRef] [PubMed]
23. Kontush, A.; Lhomme, M.; Chapman, M.J. Unraveling the complexities of the HDL lipidome. *J. Lipid Res.* **2013**, *54*, 2950–2963. [CrossRef] [PubMed]
24. Birner-Gruenberger, R.; Schittmayer, M.; Holzer, M.; Marsche, G. Understanding high-density lipoprotein function in disease: Recent advances in proteomics unravel the complexity of its composition and biology. *Prog. Lipid Res.* **2014**, *56*, 36–46. [CrossRef] [PubMed]
25. Kontush, A.; Lindahl, M.; Lhomme, M.; Calabresi, L.; Chapman, M.J.; Davidson, W.S. Structure of HDL: Particle subclasses and molecular components. *Handb. Exp. Pharmacol.* **2015**, *224*, 3–51. [CrossRef] [PubMed]
26. Kostner, G.; Alaupovic, P. Composition and structure of plasma lipoproteins. Separation and quantification of the lipoprotein families occurring in the high density lipoproteins of human plasma. *Biochemistry* **1972**, *11*, 3419–3428. [CrossRef] [PubMed]
27. Wang, N.; Silver, D.L.; Costet, P.; Tall, A.R. Specific binding of ApoA-I, enhanced cholesterol efflux, and altered plasma membrane morphology in cells expressing ABC1. *J. Biol. Chem.* **2000**, *275*, 33053–33058. [CrossRef]
28. Fernández-Hernando, C. Antiatherogenic Properties of High-Density Lipoprotein-Enriched MicroRNAs. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, e13–e14. [CrossRef]

29. Kontush, A.; Chapman, M.J. Antiatherogenic small, dense HDL—guardian angel of the arterial wall? *Nat. Clin. Pract. Cardiovasc. Med.* **2006**, *3*, 144–153. [[CrossRef](#)]
30. Duriez, P.; Fruchart, J.C. High-density lipoprotein subclasses and apolipoprotein A-I. *Clin. Chim. Acta Int. J. Clin. Chem.* **1999**, *286*, 97–114. [[CrossRef](#)]
31. Litvinov, D.; Mahini, H.; Garelnabi, M. Antioxidant and Anti-Inflammatory Role of Paraoxonase 1: Implication in Arteriosclerosis Diseases. *N. Am. J. Med. Sci.* **2012**, *4*, 523–532. [[CrossRef](#)]
32. Serna, J.; García-Seisdedos, D.; Alcázar, A.; Lasunción, M.Á.; Busto, R.; Pastor, Ó. Quantitative lipidomic analysis of plasma and plasma lipoproteins using MALDI-TOF mass spectrometry. *Chem. Phys. Lipids* **2015**, *189*, 7–18. [[CrossRef](#)] [[PubMed](#)]
33. Yetukuri, L.; Söderlund, S.; Koivuniemi, A.; Seppänen-Laakso, T.; Niemelä, P.S.; Hyvönen, M.; Taskinen, M.-R.; Vattulainen, I.; Jauhiainen, M.; Oresic, M. Composition and lipid spatial distribution of HDL particles in subjects with low and high HDL-cholesterol. *J. Lipid Res.* **2010**, *51*, 2341–2351. [[CrossRef](#)] [[PubMed](#)]
34. Wiesner, P.; Leidl, K.; Boettcher, A.; Schmitz, G.; Liebisch, G. Lipid profiling of FPLC-separated lipoprotein fractions by electrospray ionization tandem mass spectrometry. *J. Lipid Res.* **2009**, *50*, 574–585. [[CrossRef](#)] [[PubMed](#)]
35. Jonas, A.; Kézdy, K.E.; Wald, J.H. Defined apolipoprotein A-I conformations in reconstituted high density lipoprotein discs. *J. Biol. Chem.* **1989**, *264*, 4818–4824.
36. Woudberg, N.J.; Pedretti, S.; Lecour, S.; Schulz, R.; Vuilleumier, N.; James, R.W.; Frias, M.A. Pharmacological Intervention to Modulate HDL: What Do We Target? *Front. Pharmacol.* **2018**, *8*, 989. [[CrossRef](#)]
37. De la Llera-Moya, M.; Drazul-Schrader, D.; Asztalos, B.F.; Cuchel, M.; Rader, D.J.; Rothblat, G.H. The Ability to Promote Efflux via ABCA1 Determines the Capacity of Serum Specimens with Similar HDL-C to Remove Cholesterol from Macrophages. *Arterioscler. Thromb. Vasc. Biol.* **2010**, *30*, 796–801. [[CrossRef](#)]
38. Davidson, W.S.; Silva, R.A.G.D.; Chantepie, S.; Lagor, W.R.; Chapman, M.J.; Kontush, A. Proteomic analysis of defined HDL subpopulations reveals particle-specific protein clusters: Relevance to antioxidative function. *Arterioscler. Thromb. Vasc. Biol.* **2009**, *29*, 870–876. [[CrossRef](#)]
39. Christoffersen, C.; Obinata, H.; Kumaraswamy, S.B.; Galvani, S.; Ahnström, J.; Sevvana, M.; Egerer-Sieber, C.; Muller, Y.A.; Hla, T.; Nielsen, L.B.; et al. Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 9613–9618. [[CrossRef](#)]
40. Nofer, J.R.; Van Der Giet, M.; Tölle, M.; Wolinska, I.; von Wnuck Lipinski, K.; Baba, H.A.; Tietge, U.J.; Gödecke, A.; Ishii, I.; Kleuser, B.; et al. HDL induces NO-dependent vasorelaxation via the lysophospholipid receptor S1P<sub>3</sub>. *J. Clin. Investig.* **2004**, *113*, 569–581. [[CrossRef](#)]
41. Argraves, K.M.; Gazzolo, P.J.; Groh, E.M.; Wilkerson, B.A.; Matsuura, B.S.; Twal, W.O.; Hammad, S.M.; Argraves, W.S. High Density Lipoprotein-associated Sphingosine 1-Phosphate Promotes Endothelial Barrier Function. *J. Biol. Chem.* **2008**, *283*, 25074–25081. [[CrossRef](#)]
42. Ouimet, M.; Barrett, T.J.; Fisher, E.A. HDL and Reverse Cholesterol Transport. *Circ. Res.* **2019**, *124*, 1505–1518. [[CrossRef](#)] [[PubMed](#)]
43. Attie, A.D.; Kastelein, J.P.; Hayden, M.R. Pivotal role of ABCA1 in reverse cholesterol transport influencing HDL levels and susceptibility to atherosclerosis. *J. Lipid Res.* **2001**, *42*, 1717–1726. [[PubMed](#)]
44. Tang, C.; Oram, J.F. The cell cholesterol exporter ABCA1 as a protector from cardiovascular disease and diabetes. *Biochim. Biophys. Acta BBA-Mol. Cell Biol. Lipids* **2009**, *1791*, 563–572. [[CrossRef](#)] [[PubMed](#)]
45. Wang, N.; Lan, D.; Chen, W.; Matsuura, F.; Tall, A.R. ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to high-density lipoproteins. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 9774–9779. [[CrossRef](#)]
46. Kennedy, M.A.; Barrera, G.C.; Nakamura, K.; Baldán, Á.; Tarr, P.; Fishbein, M.C.; Frank, J.; Francone, O.L.; Edwards, P.A. ABCG1 has a critical role in mediating cholesterol efflux to HDL and preventing cellular lipid accumulation. *Cell Metab.* **2005**, *1*, 121–131. [[CrossRef](#)]
47. Rothblat, G.H.; Phillips, M.C. High-density lipoprotein heterogeneity and function in reverse cholesterol transport. *Curr. Opin. Lipidol.* **2010**, *21*, 229. [[CrossRef](#)]
48. Phillips, M.C.; Johnson, W.J.; Rothblat, G.H. Mechanisms and Consequences of Cellular Cholesterol Exchange and Transfer. Available online: <https://pubmed.ncbi.nlm.nih.gov/3297153/> (accessed on 14 October 2020).

49. Marsche, G.; Heine, G.H.; Stadler, J.T.; Holzer, M. Current Understanding of the Relationship of HDL Composition, Structure and Function to Their Cardioprotective Properties in Chronic Kidney Disease. *Biomolecules* **2020**, *10*, 1348. [[CrossRef](#)]
50. Assmann, G.; Gotto, A.M. HDL Cholesterol and Protective Factors in Atherosclerosis. *Circulation* **2004**, *109*, III-8–III-14. [[CrossRef](#)]
51. Nofer, J.-R.; Assmann, G. Atheroprotective effects of high-density lipoprotein-associated lysosphingolipids. *Trends Cardiovasc. Med.* **2005**, *15*, 265–271. [[CrossRef](#)]
52. Nofer, J.-R.; Kehrel, B.; Fobker, M.; Levkau, B.; Assmann, G.; von Eckardstein, A. HDL and arteriosclerosis: Beyond reverse cholesterol transport. *Atherosclerosis* **2002**, *161*, 1–16. [[CrossRef](#)]
53. Navab, M.; Ananthramaiah, G.M.; Reddy, S.T.; Van Lenten, B.J.; Ansell, B.J.; Fonarow, G.C.; Vahabzadeh, K.; Hama, S.; Hough, G.; Kamranpour, N.; et al. The oxidation hypothesis of atherogenesis: The role of oxidized phospholipids and HDL. *J. Lipid Res.* **2004**, *45*, 993–1007. [[CrossRef](#)] [[PubMed](#)]
54. Mineo, C.; Deguchi, H.; Griffin, J.H.; Shaul, P.W. Endothelial and antithrombotic actions of HDL. *Circ. Res.* **2006**, *98*, 1352–1364. [[CrossRef](#)] [[PubMed](#)]
55. Norata, G.D.; Callegari, E.; Inoue, H.; Catapano, A.L. HDL3 Induces Cyclooxygenase-2 Expression and Prostacyclin Release in Human Endothelial Cells Via a p38 MAPK/CRE-Dependent Pathway: Effects on COX-2/PGI-Synthase Coupling. *Arterioscler. Thromb. Vasc. Biol.* **2004**, *24*, 871–877. [[CrossRef](#)] [[PubMed](#)]
56. Beitz, J.; Förster, W. Influence of human low density and high density lipoprotein cholesterol on the in vitro prostaglandin I<sub>2</sub> synthetase activity. *Biochim. Biophys. Acta BBA-Lipids Lipid Metab.* **1980**, *620*, 352–355. [[CrossRef](#)]
57. Drew, B.G.; Fidge, N.H.; Gallon-Beaumier, G.; Kemp, B.E.; Kingwell, B.A. High-density lipoprotein and apolipoprotein AI increase endothelial NO synthase activity by protein association and multisite phosphorylation. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 6999–7004. [[CrossRef](#)]
58. Li, X.-A.; Titlow, W.B.; Jackson, B.A.; Giltiay, N.; Nikolova-Karakashian, M.; Uittenbogaard, A.; Smart, E.J. High density lipoprotein binding to scavenger receptor, Class B, type I activates endothelial nitric-oxide synthase in a ceramide-dependent manner. *J. Biol. Chem.* **2002**, *277*, 11058–11063. [[CrossRef](#)]
59. Yuhanna, I.S.; Zhu, Y.; Cox, B.E.; Hahner, L.D.; Osborne-Lawrence, S.; Lu, P.; Marcel, Y.L.; Anderson, R.G.; Mendelsohn, M.E.; Hobbs, H.H.; et al. High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase. *Nat. Med.* **2001**, *7*, 853–857. [[CrossRef](#)]
60. Van Linthout, S.; Spillmann, F.; Lorenz, M.; Meloni, M.; Jacobs, F.; Egorova, M.; Stangl, V.; De Geest, B.; Schultheiss, H.P.; Tschöpe, C. Vascular-Protective Effects of High-Density Lipoprotein Include the Downregulation of the Angiotensin II Type 1 Receptor. *Hypertension* **2009**, *53*, 682–687. [[CrossRef](#)]
61. Chen, W.; Xiao, H.; Rizzo, A.N.; Zhang, W.; Mai, Y.; Ye, M. Endothelial nitric oxide synthase dimerization is regulated by heat shock protein 90 rather than by phosphorylation. *PLoS ONE* **2014**, *9*, e105479. [[CrossRef](#)]
62. Panzenböck, U.; Stocker, R. Formation of methionine sulfoxide-containing specific forms of oxidized high-density lipoproteins. *Biochim. Biophys. Acta BBA-Proteins Proteom.* **2005**, *1703*, 171–181. [[CrossRef](#)]
63. Garner, B.; Waldeck, A.R.; Witting, P.K.; Rye, K.A.; Stocker, R. Oxidation of high density lipoproteins. II. Evidence for direct reduction of lipid hydroperoxides by methionine residues of apolipoproteins AI and AII. *J. Biol. Chem.* **1998**, *273*, 6088–6095. [[CrossRef](#)] [[PubMed](#)]
64. Aviram, M.; Billecke, S.; Sorenson, R.; Bisgaier, C.; Newton, R.; Rosenblat, M.; Erogul, J.; Hsu, C.; Dunlop, C.; La Du, B. Paraoxonase active site required for protection against LDL oxidation involves its free sulfhydryl group and is different from that required for its arylesterase/paraoxonase activities: Selective action of human paraoxonase allozymes Q and R. *Arterioscler. Thromb. Vasc. Biol.* **1998**, *18*, 1617–1624. [[CrossRef](#)] [[PubMed](#)]
65. Miyata, M.; Smith, J.D. Apolipoprotein E allele-specific antioxidant activity and effects on cytotoxicity by oxidative insults and beta-amyloid peptides. *Nat. Genet.* **1996**, *14*, 55–61. [[CrossRef](#)] [[PubMed](#)]
66. Kontush, A.; Chapman, M.J. Functionally defective high-density lipoprotein: A new therapeutic target at the crossroads of dyslipidemia, inflammation, and atherosclerosis. *Pharmacol. Rev.* **2006**, *58*, 342–374. [[CrossRef](#)]
67. Goulinet, S.; Chapman, M.J. Plasma LDL and HDL subspecies are heterogenous in particle content of tocopherols and oxygenated and hydrocarbon carotenoids. Relevance to oxidative resistance and atherogenesis. *Arterioscler. Thromb. Vasc. Biol.* **1997**, *17*, 786–796. [[CrossRef](#)]



68. Navab, M.; Imes, S.S.; Hama, S.Y.; Hough, G.P.; Ross, L.A.; Bork, R.W.; Valente, A.J.; Berliner, J.A.; Drinkwater, D.C.; Laks, H. Monocyte transmigration induced by modification of low density lipoprotein in cocultures of human aortic wall cells is due to induction of monocyte chemotactic protein 1 synthesis and is abolished by high density lipoprotein. *J. Clin. Investig.* **1991**, *88*, 2039–2046. [[CrossRef](#)]
69. Cockerill, G.W.; Rye, K.A.; Gamble, J.R.; Vadas, M.A.; Barter, P.J. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. *Arterioscler. Thromb. Vasc. Biol.* **1995**, *15*, 1987–1994. [[CrossRef](#)]
70. Calabresi, L.; Franceschini, G.; Sirtori, C.R.; De Palma, A.; Saresella, M.; Ferrante, P.; Taramelli, D. Inhibition of VCAM-1 expression in endothelial cells by reconstituted high density lipoproteins. *Biochem. Biophys. Res. Commun.* **1997**, *238*, 61–65. [[CrossRef](#)]
71. Bursill, C.A.; Castro, M.L.; Beattie, D.T.; Nakhla, S.; van der Vorst, E.; Heather, A.K.; Barter, P.J.; Rye, K.-A. High-density lipoproteins suppress chemokines and chemokine receptors in vitro and in vivo. *Arterioscler. Thromb. Vasc. Biol.* **2010**, *30*, 1773–1778. [[CrossRef](#)]
72. Wilson, P.W.; Abbott, R.D.; Castelli, W.P. High density lipoprotein cholesterol and mortality. The Framingham Heart Study. *Arterioscler. Off. J. Am. Heart Assoc. Inc.* **1988**, *8*, 737–741. [[CrossRef](#)]
73. Madsen, C.M.; Varbo, A.; Nordestgaard, B.G. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: Two prospective cohort studies. *Eur. Heart J.* **2017**, *38*, 2478–2486. [[CrossRef](#)] [[PubMed](#)]
74. Tall, A.R.; Yvan-Charvet, L.; Wang, N. The failure of torcetrapib: Was it the molecule or the mechanism? *Arterioscler. Thromb. Vasc. Biol.* **2007**, *27*, 257–260. [[CrossRef](#)] [[PubMed](#)]
75. Nissen, S.E.; Tardif, J.-C.; Nicholls, S.J.; Revkin, J.H.; Shear, C.L.; Duggan, W.T.; Ruzylo, W.; Bachinsky, W.B.; Lasala, G.P.; Lasala, G.P.; et al. Effect of torcetrapib on the progression of coronary atherosclerosis. *N. Engl. J. Med.* **2007**, *356*, 1304–1316. [[CrossRef](#)] [[PubMed](#)]
76. Kastelein, J.J.P.; van Leuven, S.I.; Burgess, L.; Evans, G.W.; Kuivenhoven, J.A.; Barter, P.J.; Revkin, J.H.; Grobbee, D.E.; Riley, W.A.; Shear, C.L.; et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N. Engl. J. Med.* **2007**, *356*, 1620–1630. [[CrossRef](#)]
77. Marsche, G.; Saemann, M.D.; Heinemann, A.; Holzer, M. Inflammation alters HDL composition and function: Implications for HDL-raising therapies. *Pharmacol. Ther.* **2013**, *137*, 341–351. [[CrossRef](#)]
78. Rayner, K.J.; Esau, C.C.; Hussain, F.N.; McDaniel, A.L.; Marshall, S.M.; van Gils, J.M.; Ray, T.D.; Sheedy, F.J.; Goedeke, L.; Liu, X.; et al. Inhibition of miR-33a/b in non-human primates raises plasma HDL and reduces VLDL triglycerides. *Nature* **2011**, *478*, 404–407. [[CrossRef](#)]
79. Sacks, F.M.; Rudel, L.L.; Conner, A.; Akeefe, H.; Kostner, G.; Baki, T.; Rothblat, G.; de la Llera-Moya, M.; Asztalos, B.; Perlman, T.; et al. Selective delipidation of plasma HDL enhances reverse cholesterol transport in vivo. *J. Lipid Res.* **2009**, *50*, 894–907. [[CrossRef](#)]
80. Hovingh, G.K.; Smits, L.P.; Stefanutti, C.; Soran, H.; Kwok, S.; de Graaf, J.; Gaudet, D.; Keyserling, C.H.; Klepp, H.; Frick, J.; et al. The effect of an apolipoprotein A-I-containing high-density lipoprotein-mimetic particle (CER-001) on carotid artery wall thickness in patients with homozygous familial hypercholesterolemia: The Modifying Orphan Disease Evaluation (MODE) study. *Am. Heart J.* **2015**, *169*, 736–742.e1. [[CrossRef](#)]
81. Parolini, C.; Marchesi, M.; Lorenzon, P.; Castano, M.; Balconi, E.; Miragoli, L.; Chaabane, L.; Morisetti, A.; Lorusso, V.; Martin, B.J.; et al. Dose-Related Effects of Repeated ETC-216 (Recombinant Apolipoprotein A-IMilano/1-Palmitoyl-2-Oleoyl Phosphatidylcholine Complexes) Administrations on Rabbit Lipid-Rich Soft Plaques: In Vivo Assessment by Intravascular Ultrasound and Magnetic Resonance Imaging. *J. Am. Coll. Cardiol.* **2008**, *51*, 1098–1103. [[CrossRef](#)]
82. Tardif, J.-C.; Grégoire, J.; L'Allier, P.L.; Ibrahim, R.; Lespérance, J.; Heinonen, T.M.; Kouz, S.; Berry, C.; Bassar, R.; Lavoie, M.-A.; et al. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: A randomized controlled trial. *JAMA* **2007**, *297*, 1675–1682. [[CrossRef](#)]
83. Waksman, R.; Torguson, R.; Kent, K.M.; Pichard, A.D.; Suddath, W.O.; Satler, L.F.; Martin, B.D.; Perlman, T.J.; Maltais, J.-A.B.; Weissman, N.J.; et al. A first-in-man, randomized, placebo-controlled study to evaluate the safety and feasibility of autologous delipidated high-density lipoprotein plasma infusions in patients with acute coronary syndrome. *J. Am. Coll. Cardiol.* **2010**, *55*, 2727–2735. [[CrossRef](#)] [[PubMed](#)]



84. Nissen, S.E.; Tsunoda, T.; Tuzcu, E.M.; Schoenhagen, P.; Cooper, C.J.; Yasin, M.; Eaton, G.M.; Lauer, M.A.; Sheldon, W.S.; Grines, C.L.; et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: A randomized controlled trial. *JAMA* **2003**, *290*, 2292–2300. [[CrossRef](#)] [[PubMed](#)]
85. Rohatgi, A.; Khera, A.; Berry, J.D.; Givens, E.G.; Ayers, C.R.; Wedin, K.E.; Neeland, I.J.; Yuhanna, I.S.; Rader, D.R.; de Lemos, J.A.; et al. HDL Cholesterol Efflux Capacity and Incident Cardiovascular Events. *N. Engl. J. Med.* **2014**, *371*, 2383–2393. [[CrossRef](#)] [[PubMed](#)]
86. Kosmas, C.E.; Martinez, I.; Sourlas, A.; Bouza, K.V.; Campos, F.N.; Torres, V.; Montan, P.D.; Guzman, E. High-density lipoprotein (HDL) functionality and its relevance to atherosclerotic cardiovascular disease. *Drugs Context* **2018**, *7*, 212525. [[CrossRef](#)]
87. Kosmas, C.E.; Christodoulidis, G.; Cheng, J.; Lerakis, S.; Vittorio, T.J. High-Density Lipoprotein Functionality in Coronary Artery Disease. *Am. J. Med. Sci.* **2014**, *347*, 504–508. [[CrossRef](#)]
88. Ashen, M.D.; Blumenthal, R.S. Clinical practice. Low HDL cholesterol levels. *N. Engl. J. Med.* **2005**, *353*, 1252–1260. [[CrossRef](#)]
89. Clemente-Postigo, M.; Queipo-Ortuño, M.I.; Fernandez-Garcia, D.; Gomez-Huelgas, R.; Tinahones, F.J.; Cardona, F. Adipose Tissue Gene Expression of Factors Related to Lipid Processing in Obesity. *PLoS ONE* **2011**, *6*, e24783. [[CrossRef](#)]
90. Walton, R.G.; Zhu, B.; Unal, R.; Spencer, M.; Sunkara, M.; Morris, A.J.; Charnigo, R.; Katz, W.S.; Daugherty, A.; Howatt, D.A.; et al. Increasing Adipocyte Lipoprotein Lipase Improves Glucose Metabolism in High Fat Diet-induced Obesity. *J. Biol. Chem.* **2015**, *290*, 11547–11556. [[CrossRef](#)]
91. Klop, B.; Elte, J.W.F.; Cabezas, M.C. Dyslipidemia in obesity: Mechanisms and potential targets. *Nutrients* **2013**, *5*, 1218–1240. [[CrossRef](#)]
92. Taskinen, M.-R.; Nikkilä, E.A. Lipoprotein lipase of adipose tissue and skeletal muscle in human obesity: Response to glucose and to semistarvation. *Metabolism* **1981**, *30*, 810–817. [[CrossRef](#)]
93. Feng, R.; Luo, C.; Li, C.; Du, S.; Okekunle, A.P.; Li, Y.; Chen, Y.; Zi, T.; Niu, Y. Free fatty acids profile among lean, overweight and obese non-alcoholic fatty liver disease patients: A case—Control study. *Lipids Health Dis.* **2017**, *16*, 165. [[CrossRef](#)] [[PubMed](#)]
94. Ginsberg, H.N. Insulin resistance and cardiovascular disease. *J. Clin. Investig.* **2000**, *106*, 453–458. [[CrossRef](#)] [[PubMed](#)]
95. Rashid, S.; Uffelman, K.D.; Lewis, G.F. The mechanism of HDL lowering in hypertriglyceridemic, insulin-resistant states. *J. Diabetes Complicat.* **2002**, *16*, 24–28. [[CrossRef](#)]
96. Carr, M.C.; Hokanson, J.E.; Zambon, A.; Deeb, S.S.; Barrett, P.H.; Purnell, J.Q.; Brunzell, J.D. The contribution of intraabdominal fat to gender differences in hepatic lipase activity and low/high density lipoprotein heterogeneity. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 2831–2837. [[CrossRef](#)]
97. Chatterjee, C.; Sparks, D.L. Hepatic Lipase, High Density Lipoproteins, and Hypertriglyceridemia. *Am. J. Pathol.* **2011**, *178*, 1429–1433. [[CrossRef](#)]
98. Blades, B.; Vega, G.L.; Grundy, S.M. Activities of lipoprotein lipase and hepatic triglyceride lipase in postheparin plasma of patients with low concentrations of HDL cholesterol. *Arterioscler. Thromb. J. Vasc. Biol.* **1993**, *13*, 1227–1235. [[CrossRef](#)]
99. Rashid, S.; Barrett, P.H.R.; Uffelman, K.D.; Watanabe, T.; Adeli, K.; Lewis, G.F. Lipolytically Modified Triglyceride-Enriched HDLs Are Rapidly Cleared from the Circulation. *Arterioscler. Thromb. Vasc. Biol.* **2002**, *22*, 483–487. [[CrossRef](#)]
100. Lönnqvist, F.; Nordfors, L.; Jansson, M.; Thörne, A.; Schalling, M.; Arner, P. Leptin secretion from adipose tissue in women. Relationship to plasma levels and gene expression. *J. Clin. Investig.* **1997**, *99*, 2398–2404. [[CrossRef](#)]
101. Singh, P.; Peterson, T.E.; Sert-Kuniyoshi, F.H.; Glenn, J.A.; Davison, D.E.; Romero-Corral, A.; Pusalavidyasagar, S.; Jensen, M.D.; Somers, V.K. Leptin signaling in adipose tissue: Role in lipid accumulation and weight gain. *Circ. Res.* **2012**, *111*, 599–603. [[CrossRef](#)]
102. Wu, D.M.; Shen, M.H.; Chu, N.F. Relationship between plasma leptin levels and lipid profiles among school children in Taiwan—the Taipei Children Heart Study. *Eur. J. Epidemiol.* **2001**, *17*, 911–916. [[CrossRef](#)]
103. Rainwater, D.L.; Comuzzie, A.G.; VandeBerg, J.L.; Mahaney, M.C.; Blangero, J. Serum leptin levels are independently correlated with two measures of HDL. *Atherosclerosis* **1997**, *132*, 237–243. [[CrossRef](#)]

104. Lundåsen, T.; Liao, W.; Angelin, B.; Rudling, M. Leptin induces the hepatic high density lipoprotein receptor scavenger receptor B type I (SR-BI) but not cholesterol 7 $\alpha$ -hydroxylase (Cyp7a1) in leptin-deficient (ob/ob) mice. *J. Biol. Chem.* **2003**, *278*, 43224–43228. [[CrossRef](#)] [[PubMed](#)]
105. Dullaart, R.P.F.; de Vries, R.; Dallinga-Thie, G.M.; van Tol, A.; Sluiter, W.J. Plasma cholesteryl ester transfer protein mass and phospholipid transfer protein activity are associated with leptin in type 2 diabetes mellitus. *Biochim. Biophys. Acta* **2007**, *1771*, 113–118. [[CrossRef](#)] [[PubMed](#)]
106. Radeau, T.; Lau, P.; Robb, M.; McDonnell, M.; Ailhaud, G.; McPherson, R. Cholesteryl ester transfer protein (CETP) mRNA abundance in human adipose tissue: Relationship to cell size and membrane cholesterol content. *J. Lipid Res.* **1995**, *36*, 2552–2561. [[PubMed](#)]
107. Bamba, V.; Rader, D.J. Obesity and Atherogenic Dyslipidemia. *Gastroenterology* **2007**, *132*, 2181–2190. [[CrossRef](#)]
108. Yamamoto, Y.; Hirose, H.; Saito, I.; Tomita, M.; Taniyama, M.; Matsubara, K.; Okazaki, Y.; Ishii, T.; Nishikai, K.; Saruta, T. Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. *Clin. Sci. Lond. Engl.* **2002**, *103*, 137–142. [[CrossRef](#)]
109. Ryo, M.; Nakamura, T.; Kihara, S.; Kumada, M.; Shibazaki, S.; Takahashi, M.; Nagai, M.; Matsuzawa, Y.; Funahashi, T. Adiponectin as a biomarker of the metabolic syndrome. *Circ. J. Off. J. Jpn. Circ. Soc.* **2004**, *68*, 975–981. [[CrossRef](#)]
110. Sattar, N.; Wannamethee, G.; Sarwar, N.; Tchernova, J.; Cherry, L.; Wallace, A.; Danesh, J.; Whincup, P. Adiponectin and Coronary Heart Disease. *Circulation* **2006**, *114*, 623–629. [[CrossRef](#)]
111. Cnop, M.; Havel, P.J.; Utzschneider, K.M.; Carr, D.B.; Sinha, M.K.; Boyko, E.J.; Retzlaff, B.M.; Knopp, R.H.; Brunzell, J.D.; Kahn, S.E. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: Evidence for independent roles of age and sex. *Diabetologia* **2003**, *46*, 459–469. [[CrossRef](#)]
112. Martin, L.J.; Woo, J.G.; Daniels, S.R.; Goodman, E.; Dolan, L.M. The relationships of adiponectin with insulin and lipids are strengthened with increasing adiposity. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 4255–4259. [[CrossRef](#)]
113. Baratta, R.; Amato, S.; Degano, C.; Farina, M.G.; Patanè, G.; Vigneri, R.; Frittitta, L. Adiponectin relationship with lipid metabolism is independent of body fat mass: Evidence from both cross-sectional and intervention studies. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 2665–2671. [[CrossRef](#)]
114. Després, J.P.; Couillard, C.; Gagnon, J.; Bergeron, J.; Leon, A.S.; Rao, D.C.; Skinner, J.S.; Wilmore, J.H.; Bouchard, C. Race, visceral adipose tissue, plasma lipids, and lipoprotein lipase activity in men and women: The Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) family study. *Arterioscler. Thromb. Vasc. Biol.* **2000**, *20*, 1932–1938. [[CrossRef](#)] [[PubMed](#)]
115. Carr, M.C.; Ayyobi, A.F.; Murdoch, S.J.; Deeb, S.S.; Brunzell, J.D. Contribution of hepatic lipase, lipoprotein lipase, and cholesteryl ester transfer protein to LDL and HDL heterogeneity in healthy women. *Arterioscler. Thromb. Vasc. Biol.* **2002**, *22*, 667–673. [[CrossRef](#)] [[PubMed](#)]
116. Lewis, G.F.; Lamarche, B.; Uffelman, K.D.; Heatherington, A.C.; Honig, M.A.; Szeto, L.W.; Barrett, P.H. Clearance of postprandial and lipolytically modified human HDL in rabbits and rats. *J. Lipid Res.* **1997**, *38*, 1771–1778. [[PubMed](#)]
117. Rashid, S.; Trinh, D.K.; Uffelman, K.D.; Cohn, J.S.; Rader, D.J.; Lewis, G.F. Expression of human hepatic lipase in the rabbit model preferentially enhances the clearance of triglyceride-enriched versus native high-density lipoprotein apolipoprotein A-I. *Circulation* **2003**, *107*, 3066–3072. [[CrossRef](#)] [[PubMed](#)]
118. Lewis, G.F.; Murdoch, S.; Uffelman, K.; Naples, M.; Szeto, L.; Albers, A.; Adeli, K.; Brunzell, J.D. Hepatic lipase mRNA, protein, and plasma enzyme activity is increased in the insulin-resistant, fructose-fed Syrian golden hamster and is partially normalized by the insulin sensitizer rosiglitazone. *Diabetes* **2004**, *53*, 2893–2900. [[CrossRef](#)]
119. Ishida, T.; Choi, S.; Kundu, R.K.; Hirata, K.-I.; Rubin, E.M.; Cooper, A.D.; Quertermous, T. Endothelial lipase is a major determinant of HDL level. *J. Clin. Investig.* **2003**, *111*, 347–355. [[CrossRef](#)]
120. Jin, W.; Millar, J.S.; Broedl, U.; Glick, J.M.; Rader, D.J. Inhibition of endothelial lipase causes increased HDL cholesterol levels in vivo. *J. Clin. Investig.* **2003**, *111*, 357–362. [[CrossRef](#)]
121. Ma, K.; Cilingiroglu, M.; Otvos, J.D.; Ballantyne, C.M.; Marian, A.J.; Chan, L. Endothelial lipase is a major genetic determinant for high-density lipoprotein concentration, structure, and metabolism. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 2748–2753. [[CrossRef](#)]

122. Maugeais, C.; Tietge, U.J.F.; Broedl, U.C.; Marchadier, D.; Cain, W.; McCoy, M.G.; Lund-Katz, S.; Glick, J.M.; Rader, D.J. Dose-dependent acceleration of high-density lipoprotein catabolism by endothelial lipase. *Circulation* **2003**, *108*, 2121–2126. [[CrossRef](#)]
123. Jaye, M.; Lynch, K.J.; Krawiec, J.; Marchadier, D.; Maugeais, C.; Doan, K.; South, V.; Amin, D.; Perrone, M.; Rader, D.J. A novel endothelial-derived lipase that modulates HDL metabolism. *Nat. Genet.* **1999**, *21*, 424–428. [[CrossRef](#)] [[PubMed](#)]
124. Badellino, K.O.; Wolfe, M.L.; Reilly, M.P.; Rader, D.J. Endothelial lipase concentrations are increased in metabolic syndrome and associated with coronary atherosclerosis. *PLoS Med.* **2006**, *3*, e22. [[CrossRef](#)] [[PubMed](#)]
125. De Lemos, A.S.; Wolfe, M.L.; Long, C.J.; Sivapackianathan, R.; Rader, D.J. Identification of genetic variants in endothelial lipase in persons with elevated high-density lipoprotein cholesterol. *Circulation* **2002**, *106*, 1321–1326. [[CrossRef](#)] [[PubMed](#)]
126. Castro, A.M.; Macedo-de la Concha, L.E.; Pantoja-Meléndez, C.A. Low-grade inflammation and its relation to obesity and chronic degenerative diseases. *Rev. Méd. Hosp. Gen. México* **2017**, *80*, 101–105. [[CrossRef](#)]
127. Weisberg, S.P.; McCann, D.; Desai, M.; Rosenbaum, M.; Leibel, R.L.; Ferrante, A.W. Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Investig.* **2003**, *112*, 1796–1808. [[CrossRef](#)]
128. Chung, S.; Cuffe, H.; Marshall, S.M.; McDaniel, A.L.; Ha, J.H.; Kavanagh, K.; Hong, C.; Tontonoz, P.; Temel, R.E.; Parks, J.S. Dietary Cholesterol Promotes Adipocyte Hypertrophy and Adipose Tissue Inflammation in Visceral, but Not in Subcutaneous, Fat in Monkeys. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 1880–1887. [[CrossRef](#)]
129. Kovanen, P.T.; Nikkilä, E.A.; Miettinen, T.A. Regulation of cholesterol synthesis and storage in fat cells. *J. Lipid Res.* **1975**, *16*, 211–223.
130. Farkas, J.; Angel, A.; Avigan, M.I. Studies on the compartmentation of lipid in adipose cells. II. Cholesterol accumulation and distribution in adipose tissue components. *J. Lipid Res.* **1973**, *14*, 344–356.
131. Schreiberman, P.H.; Dell, R.B. Human adipocyte cholesterol. Concentration, localization, synthesis, and turnover. *J. Clin. Investig.* **1975**, *55*, 986–993. [[CrossRef](#)]
132. Krause, B.R.; Hartman, A.D. Adipose tissue and cholesterol metabolism. *J. Lipid Res.* **1984**, *25*, 97–110.
133. McGillicuddy, F.C.; Reilly, M.P. Adipose tissue modulation of HDL. *Clin. Lipidol.* **2010**, *5*, 601–606. [[CrossRef](#)]
134. Zhang, Y.; McGillicuddy, F.C.; Hinkle, C.C.; O'Neill, S.; Glick, J.M.; Rothblat, G.H.; Reilly, M.P. Adipocyte Modulation of High-Density Lipoprotein Cholesterol. *Circulation* **2010**, *121*, 1347–1355. [[CrossRef](#)] [[PubMed](#)]
135. Woudberg, N.J.; Goedecke, J.H.; Blackhurst, D.; Frias, M.; James, R.; Opie, L.H.; Lecour, S. Association between ethnicity and obesity with high-density lipoprotein (HDL) function and subclass distribution. *Lipids Health Dis.* **2016**, *15*, 92. [[CrossRef](#)] [[PubMed](#)]
136. Woudberg, N.J.; Mendham, A.E.; Katz, A.A.; Goedecke, J.H.; Lecour, S. Exercise intervention alters HDL subclass distribution and function in obese women. *Lipids Health Dis.* **2018**, *17*, 232. [[CrossRef](#)]
137. Davidson, W.S.; Heink, A.; Sexmith, H.; Dolan, L.M.; Gordon, S.M.; Otvos, J.D.; Melchior, J.T.; Elder, D.A.; Khoury, J.; Geh, E.; et al. Obesity is associated with an altered HDL subspecies profile among adolescents with metabolic disease. *J. Lipid Res.* **2017**, *58*, 1916–1923. [[CrossRef](#)]
138. Holzer, M.; Schilcher, G.; Curcic, S.; Trieb, M.; Ljubojevic, S.; Stojakovic, T.; Scharnagl, H.; Kopecky, C.M.; Rosenkranz, A.R.; Heinemann, A.; et al. Dialysis Modalities and HDL Composition and Function. *J. Am. Soc. Nephrol.* **2015**, *26*, 2267–2276. [[CrossRef](#)]
139. Holzer, M.; Birner-Gruenberger, R.; Stojakovic, T.; El-Gamal, D.; Binder, V.; Wadsack, C.; Heinemann, A.; Marsche, G. Uremia Alters HDL Composition and Function. *J. Am. Soc. Nephrol.* **2011**, *22*, 1631–1641. [[CrossRef](#)]
140. Farbstein, D.; Levy, A.P. HDL dysfunction in diabetes: Causes and possible treatments. *Expert Rev. Cardiovasc. Ther.* **2012**, *10*, 353–361. [[CrossRef](#)]
141. Trieb, M.; Horvath, A.; Birner-Gruenberger, R.; Spindelboeck, W.; Stadlbauer, V.; Taschler, U.; Curcic, S.; Stauber, R.E.; Holzer, M.; Pasterk, L.; et al. Liver disease alters high-density lipoprotein composition, metabolism and function. *Biochim. Biophys. Acta* **2016**, *1861*, 630–638. [[CrossRef](#)]
142. Holzer, M.; Wolf, P.; Curcic, S.; Birner-Gruenberger, R.; Weger, W.; Inzinger, M.; El-Gamal, D.; Wadsack, C.; Heinemann, A.; Marsche, G. Psoriasis alters HDL composition and cholesterol efflux capacity. *J. Lipid Res.* **2012**, *53*, 1618–1624. [[CrossRef](#)]

143. Trieb, M.; Wolf, P.; Knuplez, E.; Weger, W.; Schuster, C.; Peinhaupt, M.; Holzer, M.; Trakaki, A.; Eichmann, T.; Lass, A.; et al. Abnormal composition and function of high-density lipoproteins in atopic dermatitis patients. *Allergy* **2019**, *74*, 398–402. [[CrossRef](#)] [[PubMed](#)]
144. Trakaki, A.; Sturm, G.J.; Pregartner, G.; Scharnagl, H.; Eichmann, T.O.; Trieb, M.; Knuplez, E.; Holzer, M.; Stadler, J.T.; Heinemann, A.; et al. Allergic rhinitis is associated with complex alterations in high-density lipoprotein composition and function. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **2019**, *1864*, 1280–1292. [[CrossRef](#)] [[PubMed](#)]
145. Sorrentino, S.A.; Besler, C.; Rohrer, L.; Meyer, M.; Heinrich, K.; Bahlmann, F.H.; Mueller, M.; Horváth, T.; Doerries, C.; Heinemann, M.; et al. Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. *Circulation* **2010**, *121*, 110–122. [[CrossRef](#)]
146. Perségol, L.; Vergès, B.; Foissac, M.; Gambert, P.; Duvillard, L. Inability of HDL from type 2 diabetic patients to counteract the inhibitory effect of oxidised LDL on endothelium-dependent vasorelaxation. *Diabetologia* **2006**, *49*, 1380–1386. [[CrossRef](#)] [[PubMed](#)]
147. Sasahara, T.; Nestel, P.; Fidge, N.; Sviridov, D. Cholesterol transport between cells and high density lipoprotein subfractions from obese and lean subjects. *J. Lipid Res.* **1998**, *39*, 544–554.
148. Marsche, G.; Zelzer, S.; Meinitzer, A.; Kern, S.; Meissl, S.; Pregartner, G.; Weghuber, D.; Almer, G.; Mangge, H. Adiponectin Predicts High-Density Lipoprotein Cholesterol Efflux Capacity in Adults Irrespective of Body Mass Index and Fat Distribution. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 4117–4123. [[CrossRef](#)]
149. Talbot, C.P.J.; Plat, J.; Joris, P.J.; Konings, M.; Kusters, Y.H.A.M.; Schalkwijk, C.G.; Ritsch, A.; Mensink, R.P. HDL cholesterol efflux capacity and cholesteryl ester transfer are associated with body mass, but are not changed by diet-induced weight loss: A randomized trial in abdominally obese men. *Atherosclerosis* **2018**, *274*, 23–28. [[CrossRef](#)]
150. Saleheen, D.; Scott, R.; Javad, S.; Zhao, W.; Rodrigues, A.; Picataggi, A.; Lukmanova, D.; Mucksavage, M.L.; Luben, R.; Billheimer, J.; et al. Association of HDL cholesterol efflux capacity with incident coronary heart disease events: A prospective case-control study. *Lancet Diabetes Endocrinol.* **2015**, *3*, 507–513. [[CrossRef](#)]
151. Khera, A.V.; Cuchel, M.; de la Llera-Moya, M.; Rodrigues, A.; Burke, M.F.; Jafri, K.; French, B.C.; Phillips, J.A.; Mucksavage, M.L.; Wilensky, R.L.; et al. Cholesterol Efflux Capacity, High-Density Lipoprotein Function, and Atherosclerosis. *N. Engl. J. Med.* **2011**, *364*, 127–135. [[CrossRef](#)]
152. Nigro, E.; Scudiero, O.; Monaco, M.L.; Palmieri, A.; Mazzarella, G.; Costagliola, C.; Bianco, A.; Daniele, A. New Insight into Adiponectin Role in Obesity and Obesity-Related Diseases. *BioMed Res. Int.* **2014**, *2014*. [[CrossRef](#)]
153. Ouchi, N.; Kihara, S.; Arita, Y.; Nishida, M.; Matsuyama, A.; Okamoto, Y.; Ishigami, M.; Kuriyama, H.; Kishida, K.; Nishizawa, H.; et al. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* **2001**, *103*, 1057–1063. [[CrossRef](#)] [[PubMed](#)]
154. Matsuura, F.; Oku, H.; Koseki, M.; Sandoval, J.C.; Yuasa-Kawase, M.; Tsubakio-Yamamoto, K.; Masuda, D.; Maeda, N.; Tsujii, K.; Ishigami, M.; et al. Adiponectin accelerates reverse cholesterol transport by increasing high density lipoprotein assembly in the liver. *Biochem. Biophys. Res. Commun.* **2007**, *358*, 1091–1095. [[CrossRef](#)] [[PubMed](#)]
155. Oku, H.; Matsuura, F.; Koseki, M.; Sandoval, J.C.; Yuasa-Kawase, M.; Tsubakio-Yamamoto, K.; Masuda, D.; Maeda, N.; Ohama, T.; Ishigami, M.; et al. Adiponectin deficiency suppresses ABCA1 expression and ApoA-I synthesis in the liver. *FEBS Lett.* **2007**, *581*, 5029–5033. [[CrossRef](#)] [[PubMed](#)]
156. Tsubakio-Yamamoto, K.; Matsuura, F.; Koseki, M.; Oku, H.; Sandoval, J.C.; Inagaki, M.; Nakatani, K.; Nakaoka, H.; Kawase, R.; Yuasa-Kawase, M.; et al. Adiponectin prevents atherosclerosis by increasing cholesterol efflux from macrophages. *Biochem. Biophys. Res. Commun.* **2008**, *375*, 390–394. [[CrossRef](#)]
157. Liang, B.; Wang, X.; Guo, X.; Yang, Z.; Bai, R.; Liu, M.; Xiao, C.; Bian, Y. Adiponectin upregulates ABCA1 expression through liver X receptor alpha signaling pathway in RAW 264.7 macrophages. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 450–457.
158. Chawla, A.; Boisvert, W.A.; Lee, C.-H.; Laffitte, B.A.; Barak, Y.; Joseph, S.B.; Liao, D.; Nagy, L.; Edwards, P.A.; Curtiss, L.K.; et al. A PPAR $\gamma$ -LXR-ABCA1 Pathway in Macrophages Is Involved in Cholesterol Efflux and Atherogenesis. *Mol. Cell* **2001**, *7*, 161–171. [[CrossRef](#)]



159. Vergès, B.; Petit, J.M.; Duvillard, L.; Dautin, G.; Florentin, E.; Galland, F.; Gambert, P. Adiponectin is an important determinant of apoA-I catabolism. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 1364–1369. [[CrossRef](#)]
160. Hafiane, A.; Daskalopoulou, S.S. Adiponectin's mechanisms in high-density lipoprotein biogenesis and cholesterol efflux. *Metabolism* **2020**, *113*, 154393. [[CrossRef](#)]
161. Posadas-Sánchez, R.; Posadas-Romero, C.; Mendoza-Pérez, E.; Caracas-Portilla, N.A.; Cardoso-Saldaña, G.; Medina-Urrutia, A.; Jorge-Galarza, E.; Juárez-Rojas, J.G. Cholesterol efflux and metabolic abnormalities associated with low high-density-lipoprotein-cholesterol and high triglycerides in statin-treated coronary men with low-density lipoprotein-cholesterol <70 mg/dl. *Am. J. Cardiol.* **2012**, *109*, 636–641. [[CrossRef](#)]
162. Wang, M.; Wang, D.; Zhang, Y.; Wang, X.; Liu, Y.; Xia, M. Adiponectin increases macrophages cholesterol efflux and suppresses foam cell formation in patients with type 2 diabetes mellitus. *Atherosclerosis* **2013**, *229*, 62–70. [[CrossRef](#)]
163. Clarenbach, J.; Vega, G.; Adams-Huet, B.; Considine, R.; Ricks, M.; Sumner, A. Variability in Postheparin Hepatic Lipase Activity Is Associated with Plasma Adiponectin Levels in African Americans. *J. Investig. Med. Off. Publ. Am. Fed. Clin. Res.* **2007**, *55*, 187–194. [[CrossRef](#)] [[PubMed](#)]
164. Schneider, J.G.; von Eynatten, M.; Schiekofer, S.; Nawroth, P.P.; Dugi, K.A. Low Plasma Adiponectin Levels Are Associated with Increased Hepatic Lipase Activity In Vivo: Response to Kobayashi et al. *Diabetes Care* **2006**, *29*, 181. [[CrossRef](#)]
165. Magge, S.N.; Stettler, N.; Koren, D.; Levitt Katz, L.E.; Gallagher, P.R.; Mohler, E.R.; Rader, D.J. Adiponectin is associated with favorable lipoprotein profile, independent of BMI and insulin resistance, in adolescents. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 1549–1554. [[CrossRef](#)] [[PubMed](#)]
166. Weiss, R.; Otvos, J.D.; Flyvbjerg, A.; Miserez, A.R.; Frystyk, J.; Sinnreich, R.; Kark, J.D. Adiponectin and Lipoprotein Particle Size. *Diabetes Care* **2009**, *32*, 1317–1319. [[CrossRef](#)]
167. Tsubakio-Yamamoto, K.; Sugimoto, T.; Nishida, M.; Okano, R.; Monden, Y.; Kitazume-Taneike, R.; Yamashita, T.; Nakaoka, H.; Kawase, R.; Yuasa-Kawase, M.; et al. Serum adiponectin level is correlated with the size of HDL and LDL particles determined by high performance liquid chromatography. *Metabolism* **2012**, *61*, 1763–1770. [[CrossRef](#)]
168. Shin, M.J.; Kim, O.Y. Plasma adiponectin is associated with less atherogenic lipoprotein phenotype. *Nutr. Metab. Cardiovasc. Dis.* **2011**, *21*, 770–775. [[CrossRef](#)]
169. Kobayashi, J.; Kusunoki, M.; Murase, Y.; Kawashiri, M.; Higashikata, T.; Miwa, K.; Katsuda, S.; Takata, M.; Asano, A.; Nohara, A.; et al. Relationship of Lipoprotein Lipase and Hepatic Triacylglycerol Lipase Activity to Serum Adiponectin Levels in Japanese Hyperlipidemic Men. *Horm. Metab. Res.* **2005**, *37*, 505–509. [[CrossRef](#)]
170. Von Eynatten, M.; Schneider, J.G.; Humpert, P.M.; Rudofsky, G.; Schmidt, N.; Barosch, P.; Hamann, A.; Morcos, M.; Kreuzer, J.; Bierhaus, A.; et al. Decreased plasma lipoprotein lipase in hypo adiponectinemia: An association independent of systemic inflammation and insulin resistance. *Diabetes Care* **2004**, *27*, 2925–2929. [[CrossRef](#)]
171. Van Greevenbroek, M.M.J.; Schalkwijk, C.G.; Stehouwer, C.D.A. Obesity-associated low-grade inflammation in type 2 diabetes mellitus: Causes and consequences. *Neth. J. Med.* **2013**, *71*, 174–187.
172. Monteiro, R.; Azevedo, I. Chronic Inflammation in Obesity and the Metabolic Syndrome. *Mediat. Inflamm.* **2010**, *2010*. [[CrossRef](#)]
173. Kaser, S.; Tatarczyk, T.; Stadlmayr, A.; Ciardi, C.; Röss, C.; Tschoner, A.; Sandhofer, A.; Paulweber, B.; Ebenbichler, C.F.; Patsch, J.R. Effect of obesity and insulin sensitivity on adiponectin isoform distribution. *Eur. J. Clin. Investig.* **2008**, *38*, 827–834. [[CrossRef](#)] [[PubMed](#)]
174. Meyer, L.K.; Ciaraldi, T.P.; Henry, R.R.; Wittgrove, A.C.; Phillips, S.A. Adipose tissue depot and cell size dependency of adiponectin synthesis and secretion in human obesity. *Adipocyte* **2013**, *2*, 217–226. [[CrossRef](#)] [[PubMed](#)]
175. Blachnio-Zabielska, A.U.; Koutsari, C.; Tchkonja, T.; Jensen, M.D. Sphingolipid content of human adipose tissue: Relationship to adiponectin and insulin resistance. *Obesity* **2012**, *20*, 2341–2347. [[CrossRef](#)] [[PubMed](#)]
176. Kimura, T.; Sato, K.; Kuwabara, A.; Tomura, H.; Ishiwara, M.; Kobayashi, I.; Ui, M.; Okajima, F. Sphingosine 1-phosphate may be a major component of plasma lipoproteins responsible for the cytoprotective actions in human umbilical vein endothelial cells. *J. Biol. Chem.* **2001**, *276*, 31780–31785. [[CrossRef](#)]



177. Venkataraman, K.; Lee, Y.-M.; Michaud, J.; Thangada, S.; Ai, Y.; Bonkovsky, H.L.; Parikh, N.S.; Habrukowich, C.; Hla, T. Vascular endothelium as a contributor of plasma sphingosine 1-phosphate. *Circ. Res.* **2008**, *102*, 669–676. [[CrossRef](#)]
178. Gazit, S.L.; Mariko, B.; Théron, P.; Decouture, B.; Xiong, Y.; Couty, L.; Bonnin, P.; Baudrie, V.; Le Gall, S.M.; Dizier, B.; et al. Platelet and Erythrocyte Sources of S1P Are Redundant for Vascular Development and Homeostasis, but Both Rendered Essential After Plasma S1P Depletion in Anaphylactic Shock. *Circ. Res.* **2016**, *119*, e110–e126. [[CrossRef](#)]
179. Lee, M.J.; Van Brocklyn, J.R.; Thangada, S.; Liu, C.H.; Hand, A.R.; Menzeleev, R.; Spiegel, S.; Hla, T. Sphingosine-1-phosphate as a ligand for the G protein-coupled receptor EDG-1. *Science* **1998**, *279*, 1552–1555. [[CrossRef](#)]
180. Kowalski, G.M.; Carey, A.L.; Selathurai, A.; Kingwell, B.A.; Bruce, C.R. Plasma sphingosine-1-phosphate is elevated in obesity. *PLoS ONE* **2013**, *8*, e72449. [[CrossRef](#)]
181. Majumdar, I.; Mastrandrea, L.D. Serum sphingolipids and inflammatory mediators in adolescents at risk for metabolic syndrome. *Endocrine* **2012**, *41*, 442–449. [[CrossRef](#)]
182. Green, C.L.; Mitchell, S.E.; Derous, D.; Wang, Y.; Chen, L.; Han, J.-D.J.; Promislow, D.E.L.; Lusseau, D.; Douglas, A.; Speakman, J.R. The effects of graded levels of calorie restriction: IX. Global metabolomic screen reveals modulation of carnitines, sphingolipids and bile acids in the liver of C57BL/6 mice. *Aging Cell* **2017**, *16*, 529–540. [[CrossRef](#)]
183. Silva, V.R.R.; Micheletti, T.O.; Pimentel, G.D.; Katashima, C.K.; Lenhare, L.; Morari, J.; Mendes, M.C.S.; Razolli, D.S.; Rocha, G.Z.; de Souza, C.T.; et al. Hypothalamic S1P/S1PR1 axis controls energy homeostasis. *Nat. Commun.* **2014**, *5*, 4859. [[CrossRef](#)] [[PubMed](#)]
184. Christoffersen, C.; Federspiel, C.K.; Borup, A.; Christensen, P.M.; Madsen, A.N.; Heine, M.; Nielsen, C.H.; Kjaer, A.; Holst, B.; Heeren, J.; et al. The Apolipoprotein M/S1P Axis Controls Triglyceride Metabolism and Brown Fat Activity. *Cell Rep.* **2018**, *22*, 175–188. [[CrossRef](#)] [[PubMed](#)]
185. Dahlbäck, B. Lean ApoM<sup>-/-</sup> Mice with Hyperactive Brown Adipose Tissue. *Trends Endocrinol. Metab.* **2018**, *29*, 283–284. [[CrossRef](#)] [[PubMed](#)]
186. Frej, C.; Mendez, A.J.; Ruiz, M.; Castillo, M.; Hughes, T.A.; Dahlbäck, B.; Goldberg, R.B. A Shift in ApoM/S1P Between HDL-Particles in Women With Type 1 Diabetes Mellitus Is Associated with Impaired Anti-Inflammatory Effects of the ApoM/S1P Complex. *Arterioscler. Thromb. Vasc. Biol.* **2017**, *37*, 1194–1205. [[CrossRef](#)]
187. Brolin, R.E. Bariatric surgery and long-term control of morbid obesity. *JAMA* **2002**, *288*, 2793–2796. [[CrossRef](#)]
188. Steinbrook, R. Surgery for severe obesity. *N. Engl. J. Med.* **2004**, *350*, 1075–1079. [[CrossRef](#)]
189. Kuno, T.; Tanimoto, E.; Morita, S.; Shimada, Y.J. Effects of Bariatric Surgery on Cardiovascular Disease: A Concise Update of Recent Advances. *Front. Cardiovasc. Med.* **2019**, *6*. [[CrossRef](#)]
190. Benraoune, F.; Litwin, S.E. Reductions in Cardiovascular Risk after Bariatric Surgery. *Curr. Opin. Cardiol.* **2011**, *26*, 555–561. [[CrossRef](#)]
191. Lorkowski, S.W.; Brubaker, G.; Rotroff, D.M.; Kashyap, S.R.; Bhatt, D.L.; Nissen, S.E.; Schauer, P.R.; Aminian, A.; Smith, J.D. Bariatric Surgery Improves HDL Function Examined by ApoA1 Exchange Rate and Cholesterol Efflux Capacity in Patients with Obesity and Type 2 Diabetes. *Biomolecules* **2020**, *10*, 551. [[CrossRef](#)]
192. Raffaelli, M.; Guidone, C.; Callari, C.; Iaconelli, A.; Bellantone, R.; Mingrone, G. Effect of gastric bypass versus diet on cardiovascular risk factors. *Ann. Surg.* **2014**, *259*, 694–699. [[CrossRef](#)]
193. Christou, N.V.; Sampalis, J.S.; Liberman, M.; Look, D.; Auger, S.; McLean, A.P.H.; MacLean, L.D. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. *Ann. Surg.* **2004**, *240*, 416–424. [[CrossRef](#)]
194. Williams, D.B.; Hagedorn, J.C.; Lawson, E.H.; Galanko, J.A.; Safadi, B.Y.; Curet, M.J.; Morton, J.M. Gastric bypass reduces biochemical cardiac risk factors. *Surg. Obes. Relat. Dis. Off. J. Am. Soc. Bariatr. Surg.* **2007**, *3*, 8–13. [[CrossRef](#)] [[PubMed](#)]
195. Zlabek, J.A.; Grimm, M.S.; Larson, C.J.; Mathiason, M.A.; Lambert, P.J.; Kothari, S.N. The effect of laparoscopic gastric bypass surgery on dyslipidemia in severely obese patients. *Surg. Obes. Relat. Dis. Off. J. Am. Soc. Bariatr. Surg.* **2005**, *1*, 537–542. [[CrossRef](#)] [[PubMed](#)]

196. Swarbrick, M.M.; Austrheim-Smith, I.T.; Stanhope, K.L.; Van Loan, M.D.; Ali, M.R.; Wolfe, B.M.; Havel, P.J. Circulating concentrations of high-molecular-weight adiponectin are increased following Roux-en-Y gastric bypass surgery. *Diabetologia* **2006**, *49*, 2552–2558. [[CrossRef](#)] [[PubMed](#)]
197. Kopp, H.-P.; Krzyzanowska, K.; Möhlig, M.; Spranger, J.; Pfeiffer, A.F.H.; Schernthaner, G. Effects of marked weight loss on plasma levels of adiponectin, markers of chronic subclinical inflammation and insulin resistance in morbidly obese women. *Int. J. Obes.* **2005**, *29*, 766–771. [[CrossRef](#)] [[PubMed](#)]
198. Sjöström, C.D.; Lissner, L.; Wedel, H.; Sjöström, L. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: The SOS Intervention Study. *Obes. Res.* **1999**, *7*, 477–484. [[CrossRef](#)] [[PubMed](#)]
199. Schauer, P.R.; Kashyap, S.R.; Wolski, K.; Brethauer, S.A.; Kirwan, J.P.; Pothier, C.E.; Thomas, S.; Abood, B.; Nissen, S.E.; Bhatt, D.L. Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes. *N. Engl. J. Med.* **2012**, *366*, 1567–1576. [[CrossRef](#)]
200. Schauer, P.R.; Bhatt, D.L.; Kirwan, J.P.; Wolski, K.; Brethauer, S.A.; Navaneethan, S.D.; Aminian, A.; Pothier, C.E.; Kim, E.S.H.; Nissen, S.E.; et al. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. *N. Engl. J. Med.* **2014**, *370*, 2002–2013. [[CrossRef](#)]
201. Schauer, P.R.; Bhatt, D.L.; Kirwan, J.P.; Wolski, K.; Aminian, A.; Brethauer, S.A.; Navaneethan, S.D.; Singh, R.P.; Pothier, C.E.; Nissen, S.E.; et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes—5-Year Outcomes. *N. Engl. J. Med.* **2017**, *376*, 641–651. [[CrossRef](#)]
202. Mingrone, G.; Panunzi, S.; De Gaetano, A.; Guidone, C.; Iaconelli, A.; Nanni, G.; Castagneto, M.; Bornstein, S.; Rubino, F. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet Lond. Engl.* **2015**, *386*, 964–973. [[CrossRef](#)]
203. Lorkowski, S.W.; Brubaker, G.; Li, L.; Li, X.S.; Hazen, S.L.; Smith, J.D. A Novel Cell-Free Fluorescent Assay for HDL Function: Low Apolipoprotein A1 Exchange Rate Associated with Increased Incident Cardiovascular Events. *J. Appl. Lab. Med.* **2020**, *5*, 544–557. [[CrossRef](#)] [[PubMed](#)]
204. Heffron, S.P.; Lin, B.-X.; Parikh, M.; Scolaro, B.; Adelman, S.J.; Collins, H.L.; Berger, J.S.; Fisher, E.A. Changes in High-Density Lipoprotein Cholesterol Efflux Capacity After Bariatric Surgery Are Procedure Dependent. *Arterioscler. Thromb. Vasc. Biol.* **2018**, *38*, 245–254. [[CrossRef](#)] [[PubMed](#)]
205. Zvintzou, E.; Skroubis, G.; Chroni, A.; Petropoulou, P.-I.; Gkolfinopoulou, C.; Sakellaropoulos, G.; Gantz, D.; Mihou, I.; Kalfarentzos, F.; Kypreos, K.E. Effects of bariatric surgery on HDL structure and functionality: Results from a prospective trial. *J. Clin. Lipidol.* **2014**, *8*, 408–417. [[CrossRef](#)]
206. Longitudinal Assessment of Bariatric Surgery (LABS) Consortium; Flum, D.R.; Belle, S.H.; King, W.C.; Wahed, A.S.; Berk, P.; Chapman, W.; Pories, W.; Courcoulas, A.; McCloskey, C.; et al. Perioperative safety in the longitudinal assessment of bariatric surgery. *N. Engl. J. Med.* **2009**, *361*, 445–454. [[CrossRef](#)] [[PubMed](#)]
207. Coimbra, S.; Reis, F.; Ferreira, C.; Nunes, S.; Viana, S.; Catarino, A.; Rocha-Pereira, P.; Belo, L.; Monteiro, L.; Catarino, C.; et al. Weight loss achieved by bariatric surgery modifies high-density lipoprotein subfractions and low-density lipoprotein oxidation towards atheroprotection. *Clin. Biochem.* **2019**, *63*, 46–53. [[CrossRef](#)] [[PubMed](#)]
208. Kjellmo, C.A.; Karlsson, H.; Nestvold, T.K.; Ljunggren, S.; Cederbrant, K.; Marcusson-Ståhl, M.; Mathisen, M.; Lappegård, K.T.; Hovland, A. Bariatric surgery improves lipoprotein profile in morbidly obese patients by reducing LDL cholesterol, apoB, and SAA/PON1 ratio, increasing HDL cholesterol, but has no effect on cholesterol efflux capacity. *J. Clin. Lipidol.* **2018**, *12*, 193–202. [[CrossRef](#)] [[PubMed](#)]
209. Osto, E.; Doytcheva, P.; Corteville, C.; Bueter, M.; Dörig, C.; Stivala, S.; Buhmann, H.; Colin, S.; Rohrer, L.; Hasballa, R.; et al. Rapid and body weight-independent improvement of endothelial and high-density lipoprotein function after Roux-en-Y gastric bypass: Role of glucagon-like peptide-1. *Circulation* **2015**, *131*, 871–881. [[CrossRef](#)]
210. Ding, S.; Huang, H.; Xu, Y.; Zhu, H.; Zhong, C. MiR-222 in Cardiovascular Diseases: Physiology and Pathology. *BioMed Res. Int.* **2017**, *2017*. [[CrossRef](#)]
211. Taïbi, F.; Metzinger-Le Meuth, V.; Massy, Z.A.; Metzinger, L. miR-223: An inflammatory oncomiR enters the cardiovascular field. *Biochim. Biophys. Acta BBA-Mol. Basis Dis.* **2014**, *1842*, 1001–1009. [[CrossRef](#)]
212. Ho, J.H.; Ong, K.L.; Torres, L.F.C.; Liu, Y.; Adam, S.; Iqbal, Z.; Dhage, S.; Ammori, B.J.; Syed, A.A.; Rye, K.-A.; et al. High-density lipoprotein-associated miRNA is increased following Roux-en-Y gastric bypass surgery for severe obesity. *J. Lipid Res.* **2020**, jlr.RA120000963. [[CrossRef](#)]

213. MacLean, P.S.; Wing, R.R.; Davidson, T.; Epstein, L.; Goodpaster, B.; Hall, K.D.; Levin, B.E.; Perri, M.G.; Rolls, B.J.; Rosenbaum, M.; et al. NIH working group report: Innovative research to improve maintenance of weight loss. *Obesity* **2015**, *23*, 7–15. [[CrossRef](#)] [[PubMed](#)]
214. Thomas, C.E.; Mauer, E.A.; Shukla, A.P.; Rathi, S.; Aronne, L.J. Low adoption of weight loss medications: A comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s. *Obesity* **2016**, *24*, 1955–1961. [[CrossRef](#)] [[PubMed](#)]
215. Kim, K.K.; Cho, H.-J.; Kang, H.-C.; Youn, B.-B.; Lee, K.-R. Effects on Weight Reduction and Safety of Short-Term Phentermine Administration in Korean Obese People. *Yonsei Med. J.* **2006**, *47*, 614–625. [[CrossRef](#)] [[PubMed](#)]
216. Bessesen, D.H.; Van Gaal, L.F. Progress and challenges in anti-obesity pharmacotherapy. *Lancet Diabetes Endocrinol.* **2018**, *6*, 237–248. [[CrossRef](#)]
217. Davidson, M.H.; Tonstad, S.; Oparil, S.; Schwiers, M.; Day, W.W.; Bowden, C.H. Changes in cardiovascular risk associated with phentermine and topiramate extended-release in participants with comorbidities and a body mass index  $\geq 27$  kg/m<sup>2</sup>. *Am. J. Cardiol.* **2013**, *111*, 1131–1138. [[CrossRef](#)]
218. Garvey, W.T.; Ryan, D.H.; Look, M.; Gadde, K.M.; Allison, D.B.; Peterson, C.A.; Schwiers, M.; Day, W.W.; Bowden, C.H. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): A randomized, placebo-controlled, phase 3 extension study. *Am. J. Clin. Nutr.* **2012**, *95*, 297–308. [[CrossRef](#)]
219. Mittendorfer, B.; Ostlund, R.E.; Patterson, B.W.; Klein, S. Orlistat Inhibits Dietary Cholesterol Absorption. *Obes. Res.* **2001**, *9*, 599–604. [[CrossRef](#)]
220. Berne, C.; Orlistat Swedish Type 2 diabetes Study Group. A randomized study of orlistat in combination with a weight management programme in obese patients with Type 2 diabetes treated with metformin. *Diabet. Med. J. Br. Diabet. Assoc.* **2005**, *22*, 612–618. [[CrossRef](#)]
221. Hanefeld, M.; Sachse, G. The effects of orlistat on body weight and glycaemic control in overweight patients with type 2 diabetes: A randomized, placebo-controlled trial. *Diabetes Obes. Metab.* **2002**, *4*, 415–423. [[CrossRef](#)]
222. Torgerson, J.S.; Hauptman, J.; Boldrin, M.N.; Sjörström, L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* **2004**, *27*, 155–161. [[CrossRef](#)]
223. Kelley, D.E.; Bray, G.A.; Pi-Sunyer, F.X.; Klein, S.; Hill, J.; Miles, J.; Hollander, P. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: A 1-year randomized controlled trial. *Diabetes Care* **2002**, *25*, 1033–1041. [[CrossRef](#)] [[PubMed](#)]
224. Hollander, P.A.; Elbein, S.C.; Hirsch, I.B.; Kelley, D.; McGill, J.; Taylor, T.; Weiss, S.R.; Crockett, S.E.; Kaplan, R.A.; Comstock, J.; et al. Role of Orlistat in the Treatment of Obese Patients With Type 2 Diabetes: A 1-year randomized double-blind study. *Diabetes Care* **1998**, *21*, 1288–1294. [[CrossRef](#)] [[PubMed](#)]
225. Miles, J.M.; Leiter, L.; Hollander, P.; Wadden, T.; Anderson, J.W.; Doyle, M.; Foreyt, J.; Aronne, L.; Klein, S. Effect of Orlistat in Overweight and Obese Patients With Type 2 Diabetes Treated With Metformin. *Diabetes Care* **2002**, *25*, 1123–1128. [[CrossRef](#)] [[PubMed](#)]
226. Nordestgaard, B.G.; Langsted, A.; Mora, S.; Kolovou, G.; Baum, H.; Bruckert, E.; Watts, G.F.; Sypniewska, G.; Wiklund, O.; Borén, J.; et al. Fasting is not routinely required for determination of a lipid profile: Clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur. Heart J.* **2016**, *37*, 1944–1958. [[CrossRef](#)]
227. Langsted, A.; Freiberg, J.J.; Nordestgaard, B.G. Fasting and nonfasting lipid levels: Influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. *Circulation* **2008**, *118*, 2047–2056. [[CrossRef](#)]
228. Fidler, M.C.; Sanchez, M.; Raether, B.; Weissman, N.J.; Smith, S.R.; Shanahan, W.R.; Anderson, C.M.; BLOSSOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: The BLOSSOM trial. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 3067–3077. [[CrossRef](#)]
229. O’Neil, P.M.; Smith, S.R.; Weissman, N.J.; Fidler, M.C.; Sanchez, M.; Zhang, J.; Raether, B.; Anderson, C.M.; Shanahan, W.R. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: The BLOOM-DM study. *Obesity* **2012**, *20*, 1426–1436. [[CrossRef](#)]

230. Tuccinardi, D.; Farr, O.M.; Upadhyay, J.; Oussaada, S.M.; Mathew, H.; Paschou, S.A.; Perakakis, N.; Koniaris, A.; Kelesidis, T.; Mantzoros, C.S. Lorcaserin treatment decreases body weight and improves cardiometabolic risk factors of obese adults: A 6-month-long, randomized, placebo-controlled, double-blind clinical trial. *Diabetes Obes. Metab.* **2019**, *21*, 1487–1492. [[CrossRef](#)]
231. Burcelin, R.; Gourdy, P. Harnessing glucagon-like peptide-1 receptor agonists for the pharmacological treatment of overweight and obesity. *Obes. Rev.* **2017**, *18*, 86–98. [[CrossRef](#)]
232. Christou, G.A.; Katsiki, N.; Kiortsis, D.N. The Current Role of Liraglutide in the Pharmacotherapy of Obesity. *Curr. Vasc. Pharmacol.* **2016**, *14*, 201–207. [[CrossRef](#)]
233. Engelbrechtsen, L.; Lundgren, J.; Wewer Albrechtsen, N.J.; Mahendran, Y.; Iepsen, E.W.; Finocchietto, P.; Jonsson, A.E.; Madsbad, S.; Holst, J.J.; Vestergaard, H.; et al. Treatment with liraglutide may improve markers of CVD reflected by reduced levels of apoB. *Obes. Sci. Pract.* **2017**, *3*, 425–433. [[CrossRef](#)] [[PubMed](#)]
234. D’Innocenzo, S.; Biagi, C.; Lanari, M. Obesity and the Mediterranean Diet: A Review of Evidence of the Role and Sustainability of the Mediterranean Diet. *Nutrients* **2019**, *11*, 1306. [[CrossRef](#)] [[PubMed](#)]
235. Mozaffarian, D. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity—A Comprehensive Review. *Circulation* **2016**, *133*, 187–225. [[CrossRef](#)] [[PubMed](#)]
236. Fontana, L. Calorie restriction and cardiometabolic health. *Eur. J. Cardiovasc. Prev. Rehabil.* **2008**, *15*, 3–9. [[CrossRef](#)] [[PubMed](#)]
237. Wang, Y.; Snel, M.; Jonker, J.T.; Hammer, S.; Lamb, H.J.; de Roos, A.; Meinders, A.E.; Pijl, H.; Romijn, J.A.; Smit, J.W.A.; et al. Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases plasma CETP and increases apolipoprotein AI levels without improving the cholesterol efflux properties of HDL. *Diabetes Care* **2011**, *34*, 2576–2580. [[CrossRef](#)] [[PubMed](#)]
238. Maroofi, M.; Nasrollahzadeh, J. Effect of intermittent versus continuous calorie restriction on body weight and cardiometabolic risk markers in subjects with overweight or obesity and mild-to-moderate hypertriglyceridemia: A randomized trial. *Lipids Health Dis.* **2020**, *19*, 216. [[CrossRef](#)]
239. Liang, K.-W.; Lee, W.-J.; Lee, I.-T.; Lee, W.-L.; Lin, S.-Y.; Hsu, S.-L.; Wan, C.-J.; Yu, C.-Y.; Tsai, I.-C.; Fu, C.-P.; et al. Persistent elevation of paraoxonase-1 specific enzyme activity after weight reduction in obese non-diabetic men with metabolic syndrome. *Clin. Chim. Acta* **2011**, *412*, 1835–1841. [[CrossRef](#)]
240. Kotani, K.; Sakane, N.; Sano, Y.; Tsuzaki, K.; Matsuoka, Y.; Egawa, K.; Yoshimura, M.; Horikawa, C.; Kitagawa, Y.; Kiso, Y.; et al. Changes on the physiological lactonase activity of serum paraoxonase 1 by a diet intervention for weight loss in healthy overweight and obese women. *J. Clin. Biochem. Nutr.* **2009**, *45*, 329–334. [[CrossRef](#)]
241. Shoji, T.; Nishizawa, Y.; Koyama, H.; Hagiwara, S.; Aratani, H.; Sasao, K.; Kishimoto, H.; Tanishita, H.; Morii, H. High-density-lipoprotein metabolism during a very-low-calorie diet. *Am. J. Clin. Nutr.* **1992**, *56*, 297S–298S. [[CrossRef](#)]
242. Hietanen, E.; Laitinen, M.; Ahonen, E.; Marniemi, J.; Nousiainen, U. Changes in Serum Lipids and Lecithin: Cholesterol Acyltransferase Enzyme during 1 Week Weight Reduction of Women on a Low-Calorie Diet. *Enzyme* **1983**, *29*, 160–166. [[CrossRef](#)]
243. Varady, K.A.; Bhutani, S.; Church, E.C.; Klempel, M.C. Short-term modified alternate-day fasting: A novel dietary strategy for weight loss and cardioprotection in obese adults. *Am. J. Clin. Nutr.* **2009**, *90*, 1138–1143. [[CrossRef](#)] [[PubMed](#)]
244. Varady, K.A.; Bhutani, S.; Klempel, M.C.; Kroeger, C.M.; Trepanowski, J.F.; Haus, J.M.; Hoddy, K.K.; Calvo, Y. Alternate day fasting for weight loss in normal weight and overweight subjects: A randomized controlled trial. *Nutr. J.* **2013**, *12*, 146. [[CrossRef](#)] [[PubMed](#)]
245. Stekovic, S.; Hofer, S.J.; Tripolt, N.; Aon, M.A.; Royer, P.; Pein, L.; Stadler, J.T.; Pendl, T.; Prietl, B.; Url, J.; et al. Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans. *Cell Metab.* **2019**, *30*, 462–476.e6. [[CrossRef](#)] [[PubMed](#)]
246. Bardagjy, A.S.; Steinberg, F.M. Relationship between HDL Functional Characteristics and Cardiovascular Health and Potential Impact of Dietary Patterns: A Narrative Review. *Nutrients* **2019**, *11*, 1231. [[CrossRef](#)] [[PubMed](#)]
247. Estruch, R.; Ros, E.; Salas-Salvadó, J.; Covas, M.-I.; Corella, D.; Arós, F.; Gómez-Gracia, E.; Ruiz-Gutiérrez, V.; Fiol, M.; Lapetra, J.; et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N. Engl. J. Med.* **2018**, *378*, e34. [[CrossRef](#)] [[PubMed](#)]

248. Hernáez, Á.; Castañer, O.; Elosua, R.; Pintó, X.; Estruch, R.; Salas-Salvadó, J.; Corella, D.; Arós, F.; Serra-Majem, L.; Fiol, M.; et al. Mediterranean Diet Improves High-Density Lipoprotein Function in High-Cardiovascular-Risk Individuals. *Circulation* **2017**, *135*, 633–643. [[CrossRef](#)] [[PubMed](#)]
249. Mathew, A.V.; Li, L.; Byun, J.; Guo, Y.; Michailidis, G.; Jaiswal, M.; Chen, Y.E.; Pop-Busui, R.; Pennathur, S. Therapeutic Lifestyle Changes Improve HDL Function by Inhibiting Myeloperoxidase-Mediated Oxidation in Patients With Metabolic Syndrome. *Diabetes Care* **2018**. [[CrossRef](#)]

**Publisher’s Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).