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REVIEW

Obesity and Dyslipidemia: A Review of Current Evidence

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Abstract

Purpose of Review Obesity is accompanied by atherogenic dyslipidemia, a specific lipid disorder characterized by both quantitative and qualitative changes of plasma lipoproteins. The main alterations in the lipid profile include hypertriglyceridemia, reduced high-density lipoprotein (HDL) cholesterol level, and elevated small dense low-density lipoprotein (LDL) particles. Epidemiological data show that obesity is more common in women and is a frequent risk factor for reproductive disorders, metabolic complications in pregnancy, and cardiometabolic disease later in life. The aim of this narrative review is to discuss recent advances in the research of dyslipidemia in obesity, with an emphasis on female-specific disorders and cardiometabolic risk.

Recent Findings The focus of current research on dyslipidemia in obesity is moving toward structurally and functionally modified plasma lipoproteins. Special attention is paid to the pro-atherogenic role of triglyceride-rich lipoproteins and their remnants. Introduction of advanced analytical techniques enabled identification of novel lipid biomarkers with potential clinical applications. In particular, proteomic and lipidomic studies have provided significant progress in the comprehensive research of HDL's alterations in obesity. Obesity-related dyslipidemia is a widespread metabolic disturbance in polycystic ovary syndrome patients and high-risk pregnancies, but is seldom evaluated with respect to its impact on future cardiometabolic health.

Summary Obesity and associated cardiometabolic diseases require a more depth insight into the quality of lipoprotein particles. Further application of omics-based techniques would enable a more comprehensive evaluation of dyslipidemia in order to reduce an excessive cardiovascular risk attributable to increased body weight. However, more studies on obesity-related female reproductive disorders are needed for this approach to be adopted in daily clinical practice.

Keywords Cardiovaskular risk · Small dense low-density lipoprotein · High-density lipoprotein · Remnant particles · Polycystic ovary syndrome · Pregnancy

Introduction

Obesity arises as a consequence of complex interactions between genetic susceptibility and lifestyle habits [1] and represents one of the major cardiometabolic risk factor [2]. Indeed, obesity is a central pathophysiological mechanism in the development of insulin resistance, metabolic syndrome, type 2 diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD) [3]. These conditions are often associated with disturbances in glucose and lipid metabolism that further increase the risk of cardiovascular disease (CVD) development [4]. Among them, metabolic syndrome can be considered as a potentially reversible disorder if associated risk factors are timely recognized and comprehensively managed. It is generally characterized by abdominal obesity, associated with two additional metabolic abnormalities, including hypertension, impaired glucose tolerance, or dyslipidemia [5]. Obesity-related dyslipidemia is commonly classified as an atherogenic lipoprotein phenotype [6]. This specific pattern of dyslipidemia is driven by insulin resistance and it is manifested by elevated triglycerides (TG) and reduced high-density lipoprotein cholesterol (HDL-C) level, accompanied by qualitative abnormalities of low-density lipoprotein (LDL) and HDL particles [7]. However, due to a limited availability of the methods for lipoprotein particles characterization, clinical evaluation of dyslipidemia in metabolic

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syndrome patients is based on the presence of hypertriglyceridemia and/or low HDL-C levels [5]. It is generally accepted that metabolic syndrome doubles the risk of ischemic cardiovascular and cerebrovascular diseases development and mortality [8]. In addition, both obesity and atherogenic dyslipidemia recently emerged as important indicators of worse outcome of COVID-19 [9].

The pandemic of obesity is one of the major clinical problems of today. A recent analysis by Boutari and Mantzoros [10] showed that overweight and obesity prevalence in the USA is around 40%, while in Europe reaches almost 60%. World Obesity Atlas 2023 projections show that half of the global population will be overweight or obese by 2035 [11]. According to a recent report on the global epidemiology of dyslipidemias, the prevalence of hypercholesterolemia in US adults is 12.4%, while 18% have low HDL-cholesterol levels [12]. In Europe, substantial differences in the prevalence of dyslipidemia were observed between the regions. The most prevalent lipid disorder is hypercholesterolemia, reaching up to 70% in some Central and Eastern European countries. This analysis also showed that although the pattern and prevalence of dyslipidemia varies between regions of the world, atherogenic dyslipidemia is a common disorder in patients with metabolic syndrome or diabetes [12].

Although the pathophysiological mechanisms involved in the development of dyslipidemia in obesity are becoming better recognized [13], the quality of obesity treatment seems to be lower [14]. Another aspect that deserves special attention is dyslipidemia screening in women. It is generally accepted that women have a lower risk of developing CVD than men. However, due to assumption of a more favorable prognosis, women are often not advised to take equally serious preventive measures. Yet, obesity is more prevalent in women [15], indicating that their cardiometabolic risk is underestimated. In line with the previous statement, dyslipidemia screening and management of specific female conditions related to increased body weight, such as polycystic ovary syndrome (PCOS) and high-risk pregnancies, need further improvement and require a comprehensive approach. In this paper, we reviewed recent advances in research of dyslipidemia in obesity with a focus on cardiometabolic health in women. Specifically, we provided a summary of recent data on atherogenic lipoproteins, emphasizing advanced lipid testing and newly discovered biomarkers. We also highlighted the importance of structural and functional characterization of HDL particles in obesity. Finally, we discussed the features of dyslipidemia in PCOS and metabolic complications of pregnancy, the two major obesity-related female reproductive disorders associated with increased risk of cardiometabolic disease later in life.

Atherogenic Lipoproteins in Obesity

Obesity is characterized by altered lipoprotein metabolism, which is mainly driven by insulin resistance and supported by the effects of pro-inflammatory adipokines, as we recently reviewed in detail [13]. In adipose tissue, insulin resistance results in enhanced lipolysis and excessive release of free fatty acids into circulation, which serve as substrates for de novo lipogenesis and enhanced formation of very low-density lipoproteins (VLDL) in the liver [16]. Both increased secretion and reduced clearance of VLDL particles from plasma ultimately lead to hypertriglyceridemia [17]. Apart from the increase in VLDL particles, obese individuals are characterized by a delayed clearance of postprandial chylomicrons and their remnants [18]. Such environment favors TG-enrichment of LDL and HDL particles by the cholesterol-ester transfer protein (CETP) [19]. Finally, their subsequent hydrolysis by the activity of hepatic lipase (HL) results in formation of small, dense LDL (sdLDL) and HDL particles, and concomitant lowering of plasma HDL-C levels [20].

The association between hypertriglyceridemia and CVD risk is well established, but the role of triglyceride-rich lipoproteins (TRLs) in atherosclerosis has only recently been clarified [21•]. Furthermore, novel studies have revealed new targets for the treatment of atherogenic dyslipidemia, such is angiopoietin-like protein 3 (ANGPTL3), which downregulates lipoprotein lipase activity and plasma clearance of TRLs [22]. Emerging studies demonstrated an increase of ANGPTL3 in obese and insulin-resistant subjects [23–26]. Conversely, a recent study by Garces et al. [27] found no differences in serum ANGPTL3 levels during the course of normal and pregnancy complicated by preeclampsia. As discussed earlier, elevated TRLs drive unfavorable remodeling of LDL particles and increased formation of sdLDL species, which bear the highest pro-atherogenic potential [7]. Yet, despite being established CVD risk factors, the sdLDL particles are not routinely assessed in clinical practice [28, 29]. Nevertheless, increasing attention has been recently paid to the advanced lipid testing due to observed discordance between the level of LDL-cholesterol (LDL-C) and the LDL particle number (LDL-P) [30]. At this point, it should be stressed that obesity is seldom accompanied by increased LDL-C levels [13], which is particularly evident in obese children and adolescents [31, 32]. More recent data in morbidly obese adolescents with normal conventional lipid profile showed unfavorable lipoprotein phenotype, reflected by significant increase in the particle number of large VLDL, which serve as direct precursors of sdLDL particles. In line with this finding, morbidly obese adolescents had elevated small LDL-P and

a lower number of HDL particles, as well as increased TG content within HDL. More importantly, these pro-atherogenic changes in lipoprotein profile were associated with early signs of cardiac remodeling [33]. Similarly, despite no apparent differences in serum LDL-C level, increased sdLDL particles and smaller LDL size have been demonstrated in metabolically unhealthy obese and overweight phenotype subjects than in their metabolically healthy counterparts [34]. A concept of metabolically healthy and unhealthy obesity has been introduced to distinguish obese subjects with and without concurrent cardiometabolic risk factors [35]. Yet, due to inconsistency in the criteria and transient nature, the phenomenon of metabolically healthy obesity is widely challenged in the literature. For instance, Zembic et al. [36] recently proposed a definition that does not account for dyslipidemia. Using a comprehensive metabolic profiling approach, Telle-Hansen and colleagues [37•] elegantly demonstrated substantial differences in lipoprotein profile between metabolically healthy obese and normal weigh subjects. Despite being classified as metabolically healthy obese, these subjects were characterized by higher concentrations of VLDL subclasses, but lower levels of large HDL particles than participants in normal weight group [37•]. Taken altogether, these observations confirm that effective prevention of cardiometabolic diseases requires a more depth insight into the quality of lipoprotein particles in obese subjects, starting from the childhood onwards (Table 1). Of relevance, the results of prospective the Women Health Study showed that the risk of myocardial infarction, associated with increased sdLDL-cholesterol levels, was independent of traditional risk factors and LDL-C concentration at baseline [38]. These findings highlight the clinical importance of both quantity and quality of LDL particles. It has been recently reported that higher body mass index (BMI) and serum TG concentration represent major determinants of sdLDL-cholesterol levels in patients with acute coronary syndrome [39]. Therefore, an early recognition of increased sdLDL particles, using clinical parameters and conventional lipid biomarkers, could improve prevention and reduce excessive CVD risk attributable to increased body weight.

Another common feature of obesity-related dyslipidemia is the accumulation of cholesterol-loaded remnant particles, which remain in plasma following partial lipolysis of TRLs. Remnant particles are particularly atherogenic since they can directly deliver cholesterol to subendothelial macrophages, but also due to their pro-inflammatory effects [40]. In addition, remnant particles have recently been hypothesized to contribute to impaired insulin signaling in obesity [41], suggesting the possibility for the formation of positive feedback loops. Several recent studies showed increased remnant cholesterol levels in both obese adult and pediatric populations [42–47]. The results of prospective Copenhagen General Population Study, which followed up more than 100,000 subjects during 11 years, showed that remnant cholesterol level positively correlates with BMI. Although this study showed that increased remnant cholesterol was associated with the risk of myocardial infarction across all BMI categories, remnant cholesterol levels were the highest in obese subjects, which may account for their higher risk [42]. Based on the results of the prospective Women's Health Study, women with elevated remnant cholesterol have twofold increased risk of developing CVD and even three times higher risk of myocardial infarction [38]. In contrast to aforementioned biomarkers that require advanced lipid testing, remnant cholesterol is a readily available lipid parameter. It can be easily calculated by extracting LDL-C and HDL-C from serum total cholesterol level or directly measured by commercially available assays. Another convenient option is to evaluate non-HDL-C level, encompassing concentrations of cholesterol within all pro-atherogenic lipoprotein particles, which is recommended by the European guidelines for CVD risk assessment [48], but also as a secondary therapeutic goal, particularly in patients with hypertriglyceridemia [49]. Emerging data suggest that increased non-HDL-C level is a suitable indicator of obesity-related dyslipidemia in pediatric population [50, 51].

HDL Structure and Functionality in Obesity

Reduced serum HDL-C level is a well-known characteristic of atherogenic dyslipidemia, which is commonly seen in obese subjects [52]. However, today it is widely accepted that a full understanding of HDL's contribution to the maintenance of cardiometabolic health depends on a deeper insight into its structural and functional characteristics. Being the most complex lipoprotein particle, HDL is particularly prone to structural and consequent functional modifications in an unfavorable environment, such as obesity-driven disturbed intravascular homeostasis.

The diversity of HDL's roles mainly resides on its associated protein and lipid moieties, and significant progress in comprehensive HDL analysis was made by introducing proteomic and lipidomic studies in recent years. It was repeatedly demonstrated that variations of HDL proteome are inherent in different pathophysiological conditions. One of the novel animal model studies has revealed that short-term high-fat diet provokes HDL's proteome changes, reflected by higher turnover rates of specific HDL-associated proteins which are involved in acute phase response and complement activation [53]. Such findings imply that pro-inflammatory remodeling of HDL occurs at an early phase of diet-induced obesity. In addition, higher expression of pro-inflammatory serum amyloid A (SAA) has been confirmed in obesity [54]. Since this protein is predominantly associated with

Table 1 Summary of recent studies on dyslipidemia in obesity

First author (year)	Study design	Population characteristics	Main findings and comment
Zou et al. (2023) [45]	Cross-sectional	60 799 subjects: 34 827 men and 25 972 women	Higher levels of remnant cholesterol were associated with increased risk of metabolic syndrome. The risk was significantly higher in women than in men. Remnant cholesterol had high diagnostic accuracy for metabolic syndrome
			The study suggests that remnant cholesterol could be used as simple and economical biomarker of metabolic syndrome
Stadler et al. (2023) [65•]	Cross-sectional	220 subjects: 186 pregnant women with pre-pregnant BMI $\geq$ 29 kg/m^2 and 34 normal-weight pregnant women	Total cholesterol and HDL-C levels were lower, while TG levels higher in overweight/obese pregnant women. Cord blood TG concentration was higher in offspring of overweight/obese mothers. Cholesterol efflux capacity was increased and LCAT activity decreased in obese pregnant women. A trend toward decreased cholesterol efflux capacity and reduced LCAT activity was noticed in the neonates of overweight/obese mothers
			This study demonstrated that obesity prior pregnancy is linked to lower serum antioxidant capacity and LCAT activity in both mothers and offspring, and higher cholesterol efflux capacity in mothers
Akiyama et al. (2022) [70]	Cross-sectional	164 children: 79 boys and 85 girls	Abdominal obesity in boys and girls was associated with higher TG concentration and VLDL particle numbers. Boys with abdominal obesity had higher total LDL particle number and higher medium, small, and very small LDL particle numbers, while lower large and very large HDL particle number compared to those without abdominal obesity. Girls with abdominal obesity had lower total HDL, as well as large and very large HDL particle numbers
			This study demonstrated that advanced lipid testing may improve assessment of cardiometabolic risk in obese children
Paola Gutiérrez Castro et al. (2022) [25]	Cross-sectional	127 adolescents: 30 MHNW, 25 MUNW, 22 MUO, and 30 MHO	MHO adolescents had lover levels of pro-atherogenic lipid parameters and higher HDL-C levels than MUO group. Serum lipid parameters did not differ between MHNW and MHO adolescents. Chylomicron remnants were more abundant in MUNW than in MHNW group
			The study showed that insulin resistance is associated with delayed catabolism of TRLs, which is evident even in lean adolescents
Tong et al. (2022) [47]	Cross-sectional	5 959 children: 1 194 from rural and 4 665 from urban area	Children living in urban area had higher levels of remnant cholesterol than those living in rural area. Higher remnant cholesterol levels were associated with increased risk for abdominal obesity
			The study demonstrated that evaluation of remnant cholesterol levels in children could improve prevention of cardiometabolic diseases
Siurana et al. (2022) [33]	Cross-sectional	67 adolescents: 42 obese and 22 normal weight	Obese adolescents had lower HDL-C, but higher TG and remnant cholesterol levels than normal-weight peers. Advanced lipid testing showed elevated VLDL and small LDL particles. Total HDL particles were reduced, but TG-enriched
			The study found that pro-aterogenic changes in lipoprotein profile were associated with early signs of cardiac remodeling
Wei et al. (2022) [44]	Cross-sectional	504 subjects: 229 with normal WHR and 275 with increased WHR	Subjects with WHR-defined obesity had increased remnant cholesterol, higher VLDL, and lower HDL particle concentrations than normal WHR group. No differences in LDL particle concentration or LDL-C level were found
			The study demonstrated that advanced lipid testing might improve residual risk assessment in subjects with central obesity

Table 1 (continued)

First author (year)	Study design	Population characteristics	Main findings and comment
Stadler et al. (2021) [62•]	Cross-sectional	68 female subjects: 26 normal weight, 22 overweight, and 20 obese	Decreased free cholesterol and phospholipids content of HDL particles, while increased HDL-associated cholesteryl esters in obese compared to normal weight women. Decreased apoA-I and increased SAA levels in obese subjects. Redistribution of HDL particles toward smaller HDL 3 subclasses in obese women compared to the normal-weight group. Elevated LCAT and CETP activities in obese women, when compared to their normal-weight counterparts
			This study shows that obesity induces substantial changes in HDL proteome and lipidome, HDL-modeling enzymes, and HDL subclasses' distribution
Murawska et al. (2021) [23]	Cross-sectional	238 subjects: 143 men and 95 women; ~ 22% obese	Obese men and women had lower HDL-C, but higher TG and remnant cholesterol levels than their normal weight counterparts. Obese men had increased ANGPTL3 levels, while ANGPTL8 was increased in obese women
			The study showed gender-dependent differences in ANGPTL3 and ANGPTL8 levels and pro-atherogenic lipid parameters
Lejawa et al. (2021) [24]	Cross-sectional	98 subjects: 49 MHNW, 27 MHO, and 22 MUO	MHO subjects had higher total- and LDL-C, TG, apoB, and ANGPTL3 levels, but lower HDL-C and apoA-I concentrations than MHNW. Compared to MUO group, MHO subjects had higher HDL-C and lower levels of TG, apoB, and ANGPTL3
			The study demonstrated that MHO is intermediate risk state
Janac et al. (2020) [34]	Cross-sectional	115 subjects: 38 MU and 18 MH overweigh, 43MUO, and 16 MHO	No differences in total- and LDL-C levels between metabolically healthy and unhealthy phenotypes. Metabolically unhealthy overweight and obese subjects had higher TG than their metabolically healthy counterparts. Both metabolically unhealthy groups had smaller LDL particles, higher proportion of small HDL 3, and oxidized HDL particles
			The study suggests oxidized HDL/HDL-C ratio as an indicator of disturbed metabolic health in overweight and obese subjects
Hirschler et al. (2020) [51]	Cross-sectional	1 249 children: 719 normal-weight and 530 overweight and obese	Overweight and obese children had lower HDL-C, but higher non-HDL-C levels than normal-weight children. Serum iron levels were decreased in overweight and obese children
			The study showed that increased body weight in children is associated with the risk of anemia and cardiometabolic diseases
Varbo et al. (2018) [42]	Prospective	106 216 subjects	Positive correlation between remnant cholesterol levels and BMI. Remnant cholesterol levels ≥ 1.5 mmol/L were associated with twofold higher risk for myocardial infarction in normal weight, overweight, and obese subjects
			The study suggests that association between remnant cholesterol levels and risk for myocardial infarction is independent of obesity
Nass et al. (2018) [63]	Cross-sectional	348 subjects: 147 with FLI ≥ 60	Elevated LCAT and PLTP activity in subjects with FLI ≥ 60, as a surrogate for the presence of NAFLD. LCAT and PLTP activities were associated with FLI independently of the presence of type 2 diabetes mellitus, metabolic syndrome, WHR, and insulin resistance surrogate marker HOMA-IR
			This study suggests that elevated LCAT and PLTP in NAFLD could contribute to increased risk for atherosclerosis development

HDL-C high-density lipoprotein cholesterol, *TG* triglycerides, *apoB* apolipoprotein B, *LDL-C* low-density lipoprotein cholesterol, *apoA-I* apolipoprotein A-I, *MHNW* metabolically healthy normal-weight, *MUNW* metabolically unhealthy normal-weight, *MHO* metabolically healthy obese, *MUO* metabolically unhealthy obese, *ANGPTL3* angiopoietin-like protein 3, *ANGPTL8* angiopoietin-like protein 8, *TRLs* triglyceride-rich lipoproteins, *BMI* body mass index, *WHR* waist-to-hip ratio, *VLDL* very low density lipoproteins, *FLI* fatty liver index, *NAFLD* non-alcoholic fatty liver disease, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *SAA* serum amyloid A, *LCAT* lecithin:cholesterol acyltransferase, *PLTP* phospholipid transfer protein, *GDM* gestational diabetes mellitus

HDL in circulation, it also contributes to the formation of dysfunctional HDL particles [55]. To be precise, abundant SAA replaces apolipoprotein A-I (apoA-I) on HDL particles and it should be emphasized that apoA-I is among the most important determinants of HDL functionality [56]. However, apoA-I is major, but not the only apolipoprotein within HDL. Many other apolipoproteins play structural and functional roles in associations with HDL particles. More recent research points toward apoM as a significant contributor to altered HDL functionality in obese subjects, due to its role in enabling the association between HDL and sphingosine-1-phosphate (S1P), which is a highly potent bioactive molecule [13].

Another important component of HDL proteome, vital for its antioxidative function, is paraoxonase-1 (PON1) [57]. Decreased PON1 level was found in obese men [58], whereas decreased arylesterase activity of PON1 was observed in severely obese women [59]. It has been shown that both genetic and epigenetic mechanisms are involved in deregulation of PON1 activity in NAFLD [60]. Although our research group did not find significant differences in PON1 activity in patients with increased fatty liver index (FLI) as a surrogate marker of NAFLD, we observed decreased activity of another HDL-associated antioxidative enzyme, paraoxonase 3, in subjects with higher FLI [61]. In line with this, increased level of oxidized HDL was also observed in obese individuals and proposed as a marker of metabolically unhealthy overweight and obese phenotype [34].

In parallel with the majority of other components of HDL proteome, proteins that are crucial for HDL particle remodeling, namely lecithin:cholesterol acyltransferase (LCAT) and CETP, undergo significant changes in obese individuals. Increased activity of LCAT was observed in obese women [62•], as well as patents with elevated FLI [61, 63]. Notably, the opposite results have also been recorded. Namely, negative correlation of LCAT with BMI was observed in patients with metabolic syndrome [64], while decreased LCAT activity was found in overweight and obese pregnant women and their offspring [65•]. Increased CETP concentration and activity were reported in obese subjects [20, 62•], which is in accordance with obesity-associated hypertriglyceridemia and enhanced exchange of cholesteryl esters and TG between lipoprotein particles. Yet, it should be noted that such findings are not univocally confirmed. For example, the findings of the Netherlands Epidemiology of Obesity study suggest that serum CETP concentration is not associated with multiple markers of body fat [66]. Overexpression of yet another significant modulator of HDL structure and function, namely phospholipid transfer protein (PLTP), in obese individuals is well known, and recent evidence confirmed such findings. It has been shown that insulin sensitivity is ameliorated in PLTP knockout mice, thus protecting them from the development of high fat diet-induced obesity [67]. In addition, PLTP activity was reportedly independently associated with elevated FLI [63].

Obesity-driven alterations of HDL's modulatory proteins lead to changes of its lipid composition (Fig. 1). Lipidomic study of Mocciaro et al. [64] has revealed that HDL composition in subjects with metabolic syndrome and central obesity is characterized by the abundance of TG and sphingomyelins which contain saturated very long chain fatty acids, in parallel with the reduced presence of cholesteryl esters, specific phospholipids, lysophospholipids, and mono-unsaturated fatty acid sphingomyelins. It is important to mention that, in parallel with modification of HDL's lipid composition by its constitutive proteins, lipid moieties affect HDL proteome as well. It is well known that TG enrichment compromises the association of apoA-I to HDL, and recently, it has been shown that other lipids can also change HDL functionality. Namely, supplementation with polyunsaturated 10,12-conjugated linoleic acid reportedly improves HDL proteome and functional properties in animal models [68].

Variations of HDL proteome and lipidome in obese individuals initiate consequent structural changes of these lipoprotein particles. Indeed, decreased prevalence of large HDL subclasses was demonstrated in obese and insulin resistant adolescents [69], as well as in children with abdominal obesity [70]. Similarly, small HDL 3 subclasses were more abundant in obese adult women that in their normal weight counterparts [62•]. Novel findings of Woudberg et al. [71] implicate that distribution of HDL subclasses is shifted toward smaller particles in parallel with the increased percentage of central fat mass. In line with this, it has been shown that physical exercise and low energy diet are associated with changes of HDL subclasses distribution, specifically decreased prevalence of smaller HDL particles [72, 73]. Also, recent investigations demonstrated beneficial effects of restrictive dietary regime and physical exercise on HDL particle distribution in lactating overweight/obese women [74]. Interestingly, it has been reported that altered distribution of HDL subfractions and more abundant presence of small HDL particles are associated with higher probability to develop metabolically unhealthy obese phenotype [34, 75•]. Thus, subtle changes in HDL structure might not be merely hallmarks of obesity-related dyslipidemia but could contribute to the development of specific metabolic alterations that lead to increased cardiometabolic risk in obese subjects (Table 1).

Noteworthy, large cohort studies have revealed that high HDL-C levels are also associated with unfavorable health outcomes. Namely, a U-shaped association between HDL-C levels and overall mortality was found by investigating data from the Copenhagen City Heart Study and the Copenhagen General Population Study. Accordingly, increased hazard ratios for all-cause mortality in both sexes

were recorded for HDL-C levels above 2.5 mmol/L [76]. As more recently reviewed [77, 78], markedly elevated HDL-C is associated with cardiovascular mortality, as well as with increased risk of infectious diseases and age-related macular degeneration, while inconclusive results are yielded for the associations of elevated HDL-C and autoimmune diseases and cancer. Although the mechanisms that link high HDL-C with possible deleterious effects on human health are mostly unclear, several hypotheses were risen, including a concomitant impact of genetic factors on both HDL-C and specific pathways which are involved in the disease progression, a presence of confounding features such as increased alcohol consumption, or detrimental effects of delayed HDL catabolism [77, 78]. Importantly, changes in HDL functionality might represent underlying mechanism responsible for harmful effects of both increased and decreased serum HDL-C levels, which emphasizes the significance of HDL quality estimation.

Obesity and Dyslipidemia in Female-Specific Disorders

Females and males exhibit many specific differences in sex hormone status, metabolic processes, and risk of developing CVD, especially during women's reproductive life [79]. In the reproductive period, when estrogen concentration is high, insulin sensitivity in women is higher, while visceral fat accumulation is lower, and these metabolic specificities represent essential pieces in the puzzle of lower risk for cardiometabolic diseases development in women [80]. However, obesity and dyslipidemia can abolish these advantages in women by increasing the risk of insulin resistance development [81]. This section will discuss the effects of obesity and dyslipidemia in the pathogenesis of the most common female-specific disorders during women's reproductive life: PCOS and metabolic complications in pregnancy (gestational diabetes mellitus, gestational hypertension, and preeclampsia).

PCOS is the most common reproductive endocrine disorder in women of reproductive age, with a global prevalence of 5 to 18%, which is higher in high-income countries (Europe and the USA) and lower in the East Asian region [82, 83]. Despite much research focused on the mechanisms of PCOS development, the pathophysiology of PCOS is not entirely understood. The current concept of PCOS pathophysiology implies multiple interactions between genetic, environmental, and intra-uterine factors [84]. Clinical features of PCOS include clinical and biochemical manifestations of excessive androgen production, polycystic ovarian morphology, and anovulation (reproductive dysfunction, oligo-amenorrhoea, and lower fertility rate) [85]. Metabolic disturbances are not included in any diagnostic criteria for PCOS. Still, epidemiological data indicate that 38–88% of women with PCOS are overweight or obese, while around 75% of lean-body women with PCOS have insulin resistance, and 50% have metabolic syndrome [86, 87]. Hence, PCOS is a combination of clinical features of hyperandrogenism, reproductive, and metabolic disorders which are manifested through different PCOS phenotypes [88]. The main metabolic alteration which connects obesity and PCOS is insulin resistance and associated hyperinsulinemia, which contributes to the reproductive and endocrine features of PCOS [89]. Insulin stimulates the ovarian theca cells, acting as a co-gonadotropin, i.e., synergistically with luteinizing hormone (LH). It activates the key enzyme in ovarian testosterone biosynthesis, cytochrome P450 17 alpha-hydroxylase/17,20-lyase (CYP17), thus promoting hyperandrogenism in PCOS [90]. Furthermore, hyperinsulinemia is associated with the suppression of sex hormone binding globulin (SHBG) synthesis in the liver, which results in an increase of free, biologically active

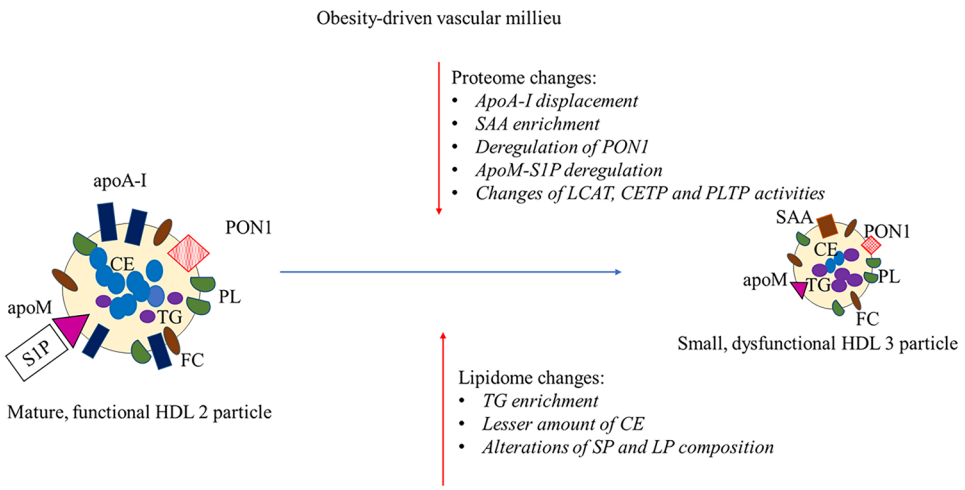

Fig. 1 Structural and functional modification of HDL proteome and lipidome in obese individuals. Abbreviations: SAA, serum amyloid A; PON1, paraoxonase-1; S1P, sphingosine-1-phosphate; CE, cholesteryl-esters; PL, phospholipids; LCAT, lecithin: cholesterol acyltransferase; CETP, cholesteryl ester transfer protein; PLTP, phospholipid transfer protein

testosterone concentration [91]. Chronic hyperinsulinemia also has a stimulatory effect on the pituitary release of LH [92]. Notably, a recent review indicated the association of elevated activity of adipose tissue 5α-reductase with obesity and insulin resistance in pathogenesis of PCOS and marked it as a specific biochemical feature of PCOS [87, 93].

Dyslipidemia is a widespread metabolic disturbance of PCOS with a prevalence of 50 to 70% [94]. Obesity, insulin resistance, and hyperandrogenism may synergistically affect lipid profile in PCOS. However, the underlying mechanism of dyslipidemia pathogenesis in PCOS is still not entirely explained. Pan et al. [95] recently showed that specific hypomethylated genes are associated with the synthesis of androgen and lipids, implicating that the association of hyperandrogenism and dyslipidemia in PCOS might be explained by epigenetic alterations. Furthermore, Spalkowska et al. [96] found that specific lipid profiles among lean PCOS patients are related to differences in androgen concentrations. Namely, patients with higher androgen levels had more atherogenic lipid profile. Dyslipidemia in PCOS patients is characterized by elevated plasma total cholesterol and TG, and decreased HDL-C concentrations, while LDL-C concentration is often slightly elevated [97]. However, the results of a recent study indicated significant changes in LDL particles distribution, especially in obese PCOS patients, which were characterized by a higher proportion of sdLDL species, indicating higher CVD risk [98]. A recent study by Vatannejad et al. [99•] demonstrated higher levels of ANGPTL3 in PCOS patients compared with healthy controls and its positive correlation with the degree of adiposity, insulin resistance, and dyslipidemia. The authors highlighted the need for further investigation of ANGPTL3 to assess its diagnostic and therapeutic potential in PCOS. Decreased HDL particle diameters and higher proportions of dysfunctional small HDL 3 subclasses were also reported in overweight and obese PCOS patients, suggesting the shift in lipoprotein particles distribution toward more atherogenic profile [98]. Samino et al. [100] found that hyperinsulinemia-associated androgen excess in both lean and obese PCOS patients is linked to apoA-I oxidation which impairs HDL maturation and attenuates its antiatherogenic properties. A recent proteomic study by Butler et al. [101] indicated dysregulation of HDL protein composition in patients with PCOS, including higher levels of apoE, complement component C3, and heparin cofactor II, but lower content of apoM. The authors acknowledged that these alterations might contribute to pro-atherogenic changes of lipid profile, but pointed out that lifestyle modifications could diminish adverse effects of obesity and dyslipidemia on cardiometabolic risk in PCOS.

The prevalence of maternal obesity before and during pregnancy has been rising worldwide in recent decades and represents one of the most important challenges in global strategies for improving pregnancy outcomes. The frequency of maternal obesity in Europe varies from 7 to 25%, and it is associated with lower maternal education level and socioeconomic status [102]. The main pregnancy complications related to maternal obesity are gestational diabetes, gestational hypertension, and preeclampsia, while the fetus is at risk of macrosomia, premature birth, stillbirth, and congenital anomalies [103, 104]. Adverse pregnancy outcomes could also affect future cardiometabolic health of both mother and child [105].

Pregnancy is physiologically associated with metabolic changes (including insulin resistance, hyperinsulinemia, and mild dyslipidemia), low-grade inflammation, and oxidative stress, which develop during the adaptation of maternal metabolism with an aim to ensure an adequate growth of the fetus [106]. On the other side, these are also the main molecular mechanisms which connect obesity and adverse pregnancy outcomes [107]. Yet, current clinical and laboratory evaluation of obesity-related pregnancy complications is focused solely on glucose homeostasis control, due to the risk for gestational diabetes and fetal macrosomia development [108]. However, additional aspects of maternal metabolism have to be considered to ensure favorable pregnancy outcome, especially obesity-related pre-pregnancy dyslipidemia.

Physiological changes in lipid metabolism are essential for fetal growth and development. They are manifested by an increase in serum levels of total cholesterol and TG, induced by estrogen, progesterone, and lactogen from the placenta, and by a substantial rise in insulin secretion due to pancreatic β-cell hyperplasia [109, 110]. Although LDL-C concentrations moderately increase, a specific feature of dyslipidemia in physiological pregnancy is a concomitant increase of HDL-C level. Namely, HDL-C reaches a peak in mid-gestation and tends to slightly decline toward the end of pregnancy, but higher levels persist even after delivery [111, 112]. Although TG have been established as the main source of fatty acids for fetal growth, maternal hypertriglyceridemia is associated with adverse outcomes for the offspring, such as macrosomia, intrauterine growth restriction, and prematurity [113]. Furthermore, hypertriglyceridemia and lower HDL-C concentration before pregnancy and during the first trimester have been connected with pancreatic β-cell dysfunction and damaged insulin action, which leads to deregulation of glucose homeostasis during pregnancy and significantly increases the risk for gestational diabetes development [114]. Recently, Ardalic et al. [115] found that the atherogenic index of plasma (AIP), calculated as base ten logarithm of plasma TG to HDL-C ratio, was associated with high-risk pregnancies and suggested this biomarker for the assessment of preeclampsia risk.

Estrogen-induced hypertriglyceridemia and elevated activity of CETP lead to the accumulation of TG in LDL

and HDL particles and consequent changes of their structure and functionality [116]. Our previous research of longitudinal changes in lipoprotein distribution during physiological pregnancies revealed a shift toward sdLDL and small HDL particles in parallel with the increase of TG concentration, as pregnancy progresses [117]. This study also showed that increased proportion of sdLDL particles in maternal plasma before delivery was an independent predictor of smaller birth size [117]. So far, LDL particle alterations in pregnancy complications have been extensively studied, and the results have been relatively consistent. Available data indicate that women with gestational diabetes, gestational hypertension, and preeclampsia have significantly increased proportion of sdLDL particles [118, 119]. Recent studies suggested a link between adverse HDL remodeling in pregnancy and development of different metabolic complications [120, 121]. In a quest for better understanding of structural and functional modifications of HDL in pregnancy complications, a deeper insight into HDL proteome and lipidome is required. Yet, results regarding apoA-I and pregnancy complications development are inconsistent [122–124]. Another potential protein biomarker is apoM, which bounds S1P within HDL. S1P has a crucial role in maternal vascular function, placental vascularization, and fetoplacental endothelial function [125]. It was shown that high apoM concentrations in the first trimester could be associated with gestational hypertension development [126]. Yet, despite a growing body of evidence on the impact of dyslipidemia to pregnancy complications, pharmacological treatment of dyslipidemia in pregnancy is not recommended by the international guidelines. Nowadays, only healthy diet and physical activity are globally accepted recommendations for improving pregnancy outcome [127, 128].

Menopausal transition and menopause, as innate stages of female reproductive life, are associated with notable alterations of hormonal status and resultant changes in body composition, energy metabolism, and serum lipid profile. Epidemiological data shows that obesity is more prevalent in women than in men [15] and recent findings demonstrated increased prevalence of obesity in menopausal women, although statistically significant differences among age groups were not reached [129]. Such observed trends arose at least in part due to perimenopausal and menopausal adjustments of woman's metabolism. A decline in estradiol production and accompanying relative hyperanderogenism are followed by a positive energy balance, weight gain, and accumulation of abdominal fat [130]. It is well established that visceral adiposity is associated with insulin resistance, which is a driving force for the development of dyslipidemia. Indeed, typical changes of serum lipid profile during the menopausal transition comprise an increase of total cholesterol, TG, and LDL-C levels, as well as elevation of total cholesterol/HDL-C ratio [131]. The results regarding HDL-C in menopause are conflicting [131], but once again it should be emphasized that qualitative changes of HDL particles are probably more relevant for the estimation of HDL's role in perimenopause and menopause, than the measurement of HDL-C level. In line with this, greater abundance of small HDL particles and declined cholesterol efflux capacity per particle were noticed during menopausal transition [132]. Furthermore, an increase of sdLDL-cholesterol levels which corresponds with menopausal transition was reported [133]. Thus, remodeling of LDL and HDL particles which occurs in perimenopause and menopause favors the development of pro-atherogenic lipoprotein phenotype and contributes to elevated cardiometabolic risk in this population.

Future Perspectives

Evaluation and treatment of dyslipidemia in obesity is one of the most important tasks for effective prevention of cardiometabolic diseases. To date, numerous national and international evidence-based clinical practice guidelines have been developed to assist healthcare professionals in selecting appropriate laboratory tests for dyslipidemia diagnosis, the most effective therapy, and specific treatment targets for monitoring response to lipid-lowering medications. Current American College of Cardiology (ACC)/American Heart Association (AHA) [134] and European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) [49] clinical practice guidelines on the management of dyslipidemia and primary prevention of CVD include specific considerations for metabolic syndrome and diabetes mellitus, the two main conditions associated with obesity (Table 2). Overall, metabolic syndrome, hypertriglyceridemia, and diabetes were recognized as risk-enhancing factors which support earlier initiation of lipid-lowering medications. Although statins remain a cornerstone of dyslipidemia treatment, in which lowering LDL-C is the main therapeutic goal, recent data suggest that innovative lipid-lowering therapeutics and certain dietary supplements may also improve LDL particle quality [22]. However, whether these novel approaches will be recommended for the treatment of atherogenic dyslipidemia in obesity remains to be seen.

Although obesity-associated dyslipidemia is a well-known clinical phenomenon, scientific community is still searching for a tool that would enable complete understanding of underlying biochemical processes. Therefore, novel analytical approaches are introduced and novel biomarkers are continuously proposed. Non-cholesterol sterols (NCS) have drawn the attention as potential biomarkers of cholesterol metabolism. Namely, serum levels of intermediates in cholesterol biosynthesis pathway, such as lathosterol or desmosterol, are useful as indicators of

endogenous cholesterol synthesis capacity, whereas circulating phytosterols' concentrations can be used as a measure of intestinal cholesterol absorption [135]. Obesity is characterized by a disruption of a delicate balance between endogenous cholesterol synthesis and absorption of dietary cholesterol. A recent meta-analysis has indicated that cholesterol homeostasis is shifted toward increased synthesis and decreased absorption in overweight and obese subjects, while diet-induced weight loss contributes to the restoration of synthesis-absorption balance [136]. Our own study demonstrated similar patterns of changes in cholesterol synthesis and absorption markers in obese patients with obstructive sleep apnea [137]. Knowing that NCS have demonstrated usefulness for evaluation of dyslipidemia types and selection of an adequate lipid-lowering therapy [138, 139], a similar approach might be applied for the assessment of metabolic alterations in obese subjects and the effectiveness of weight loss procedures. Although several recent studies analyzed changes in NCS levels after specific weight-loss procedures, current results are inconsistent [140–142]. Thus, further research in this area is warranted.

Lipidomic profiling is nowadays gaining much attention in a research of pregnancy-associated dyslipidemia. These studies enabled identification of specific lipid signature, which is typical for metabolic complications in pregnancy [143, 144•]. The newest investigations in this field have highlighted specific glycerolipids, NCS, and sphingomyelins and their specific interactions in the development of different pregnancy complications [120, 143, 145]. Further lipidomic studies should reveal additional molecular mechanism underlying pregnancy complications and hopefully

Table 2 Recommendations for the measurement of lipid status in primary prevention of CVD with reference to obesity-related conditions

2018 AHA/ACC Guideline on the management of blood cholesterol [134]	Lipid status determination and CVD risk assessment: • To estimate CVD risk and baseline LDL-C levels, complete lipid status assessment (total cholesterol, LDL-C, HDL-C, and TG) is recommended. Determination of lipid status parameters can be performed in fasting or non-fasting samples • Estimation of 10-year CVD risk is recommended for adults > 20 years of age with LDL-C level > 1.8 mmol/L • Metabolic syndrome, LDL-C level ≥ 4.1 mmol/L, and persistent TG levels ≥ 2 mmol/L are considered risk-enhancing factors which favor statin initiation. Specific cut-off points for metabolic syndrome evaluation: TG > 1.95 mmol/L, and HDL-C < 1.03 mmol/L in men or < 1.30 mmol/L in women • In adults without diabetes mellitus and with LDL-C ≥ 1.8 mmol/L, initiation of a moderate-intensity statin treatment is suggested at intermediate 10-year risk (≥ 7.5%). For patients with diabetes and LDL-C level ≥ 1.8 mmol/L, an intensive statin treatment is recommended Lipid-lowering treatment goals: • LDL-C level reduction by 30–50% from baseline, depending on the estimated CVD risk • To assess adherence and response to therapy, LDL-C level measurement is recommended 4–12 weeks after statin initiation or dose adjustment. Lipid testing should be repeated annually
2019 ESC/EAS Guidelines for the management of dyslipidaemias [49]	Lipid status and CVD risk assessment: • To estimate CVD risk, measurement of total cholesterol, HDL-C, and LDL-C is recommended. Determination of lipid status parameters can be performed in fasting or non-fasting samples • Assessment of TG level is particularly relevant in obesity, metabolic syndrome, and diabetes mellitus patients. Non-HDL-C or apolipoprotein B measurement is advised for patients with increased TG or low LDL-C levels • Estimation of 10-year CVD risk is recommended in men > 40 and in women > 50 years of age, as well as in those with LDL-C level > 4.9 mmol/L • An optimal LDL-C level for low-risk individuals is < 3 mmol/L, while TG level < 1.7 mmol/L indicates lower CVD risk • In adults with moderate 10-year risk (≥ 1 to 5%), initiation of lipid-lowering treatment is considered at LDL-C level ≥ 2.6 mmol/L and recommended at LDL-C level ≥ 4.9 mmol/L • Patients with diabetes are immediately classified in high-risk or very high-risk categories, depending on the presence of microvascular complications or additional risk factors. For patients with high-risk and LDL-C level ≥ 2.6 mmol/L, lipid-lowering therapy is recommended Lipid-lowering treatment goals: • LDL-C goal for patients with moderate risk is < 2.6 mmol/L, while those with high risk should achieve LDL-C level < 1.8 mmol/L or reduce baseline level by 50% • Non-HDL-C and apolipoprotein B levels can be considered as secondary targets, particularly in patients with diabetes • To assess response to therapy, complete lipid profile or LDL-C level assessment is recommended 6–8 weeks from initiation of therapy or dose adjustment. After the goal is achieved, lipid status should be tested annualy

AHA American Heart Organization, *ACC* American College of Cardiology, *ESC* European Society of Cardiology, *EAS* European Atherosclerosis Society, *CVD* cardiovascular disease, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides

provide more innovative approaches to improve pregnancy outcome.

Conclusions

Dyslipidemia is a prominent feature of obesity, but also one of the most important contributors to cardiometabolic complications in obese individuals. Although obesity-driven dyslipidemia is typically assessed by the determination of routine serum lipid profile, it is nowadays clear that deeper insight into lipoprotein metabolism is necessary for comprehensive evaluation of dyslipidemia-associated cardiometabolic risk. Recent evidence points toward the importance of particular lipoprotein particles in the development of atherosclerosis and other metabolic disturbances. Specifically, remnant particles, as well as structurally and functionally modified LDL and HDL subclasses, are probably even more important for the estimation of overall cardiometabolic risk than standard lipid parameters, such as TG, LDL-C, or HDL-C. The main findings of relevant studies are summarized in Table 1. Novel analytical approaches provided by multiple omics techniques enable thorough evaluation of dyslipidemia and thereby pave the way for introducing personalized diagnostics, more efficient prevention, and therapy. This could be especially important for women, having in mind the prevalence of female obesity and its involvement in the development of reproductive disorders.

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Compliance with Ethical Standards

Conflict of Interest There are no conflicts of interest to disclose.

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