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Metabolism Clinical and Experimental 92 (2019) 71–81

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Obesity and dyslipidemia

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ARTICLE INFO

Article history:
Received 27 August 2018
Received in revised form 7 November 2018
Accepted 11 November 2018

Keywords:
Insulin resistance
Adipokines
Vitamin D
Small, dense LDL
PCSK9
Sphingosine-1-phosphate
MicroRNA

ABSTRACT

Obesity, a pandemic of the modern world, is intimately associated with dyslipidemia, which is mainly driven by the effects of insulin resistance and pro-inflammatory adipokines. However, recent evidence suggests that obesity-induced dyslipidemia is not a unique pathophysiological entity, but rather has distinct characteristics depending on many individual factors. In line with that, in a subgroup of metabolically healthy obese (MHO) individuals, dyslipidemia is less prominent or even absent. In this review, we will address the main characteristics of dyslipidemia and mechanisms that induce its development in obesity. The fields, which should be further investigated to expand our knowledge on obesity-related dyslipidemia and potentially yield new strategies for prevention and management of cardiometabolic risk, will be highlighted. Also, we will discuss recent findings on novel lipid biomarkers in obesity, in particular proprotein convertase subtilisin/kexin type 9 (PCSK9), as the key molecule that regulates metabolism of low-density lipoproteins (LDL), and sphingosine-1-phosphate (S1P), as one of the most important mediators of high-density lipoprotein (HDL) particles function. Special attention will be given to microRNAs and their potential use as biomarkers of obesity-associated dyslipidemia.

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Contents

Abbreviations: FFAs, free fatty acids; LPL, lipoprotein lipase; sdLDL, small, dense low-density lipoprotein; TNF-α, tumor necrosis factor-α; PCSK9, proprotein convertase subtilisin/kexin type 9; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; S1P, sphingosine-1-phosphate.

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https://doi.org/10.1016/j.metabol.2018.11.005
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1. Introduction

Weight gain, as a response to overnutrition and reduced energy expenditure, leads to overweight and obesity, conditions associated with intensive processes of hyperplasia and hypertrophy of adipocytes [1]. Also, obesity is accompanied by macrophages infiltration into the adipose tissue, followed by a switch of their phenotype from anti-inflammatory M2 to pro-inflammatory M1 [2]. All these changes in adipose tissue composition are associated with altered adipokines secretion and development of adipose tissue dysfunction (adiposopathy) which is responsible for obesity-related metabolic diseases [3].

Insulin resistance/hyperinsulinemia is the most common metabolic disorder in obesity and it is the main driving force behind the development of dyslipidemia. In recent years, the form of dyslipidemia arising from concerted action of insulin resistance and obesity is recognized as "metabolic dyslipidemia" [4]. High concentrations of triglycerides (TG) accompanied by decreased high-density lipoprotein cholesterol (HDL-C) concentrations are its main characteristics. Low-density lipoprotein cholesterol (LDL-C) concentrations could be optimal or mildly increased, although the number of LDL particles (LDL-P) can be increased [5]. Dyslipidemia is an important link between obesity and the development of type 2 diabetes mellitus, cardiovascular disease (CVD) and certain types of cancer [6].

2. Pathways of metabolic dyslipidemia development

Accumulating evidence suggests that insulin resistance is the most probable link between obesity and obesity-associated metabolic dyslipidemia [4]. According to Magkos et al. [7] insulin resistance and metabolic dyslipidemia are associated with adiposopathy. As previously demonstrated, adiposopathy is characterised by several structural and functional changes in adipose tissue [2,3]. These abnormalities also have detrimental effects on adipocyte intracellular structure, leading to endoplasmic reticulum stress and dysfunction of mitochondria [8]. Generally, it is accepted that the most important molecular mediators of obesity-related insulin resistance are adipokines, produced by adipocytes and accumulated macrophages in adiposopathy [9]. Moreover, changed adipocytes are insulin-resistant, which increases lipolysis and release of free fatty acids (FFAs) into the circulation. Increased FFAs concentration provokes lipotoxicity, as another mechanism of obesity-related insulin resistance in non-adipose tissue [10].

2.1. Insulin resistance

Effects of insulin on lipid metabolism are known and well explained [4]. Insulin suppresses lipolysis in adipose tissue by hormone-sensitive lipase (HSL) inhibition, thereby controlling the release of FFAs into the circulation [11]. Also, insulin stimulates apolipoprotein B-100 (apoB-100) degradation and suppresses very low-density lipoproteins (VLDL) secretion from the liver [12]. In the circulation, lipoprotein lipase (LPL)-driven hydrolysis of TG from VLDL particles is stimulated by insulin, as well as the activity of hepatic lipase (HL), so overall, insulin stimulates TG-rich lipoprotein degradation. In the liver, insulin promotes dephosphorylation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, activating the enzyme and stimulating the rate of cholesterol synthesis [11]. In the state of insulin resistance, plasma clearance of TG-rich lipoproteins is delayed, resulting in hypertriglyceridemia. Under these circumstances, cholesteryl ester transfer protein (CETP) activity promotes the exchange of TG with cholesteryl esters between lipoprotein particles. As a result, LDL and HDL particles become enriched with TG and, after subsequent hydrolysis by plasma lipases, smaller and denser. These structural changes are accompanied by functional consequences, resulting in the accumulation of small, dense (sdLDL) and dysfunctional HDL particles [13].

The role of FFAs in obesity-related insulin resistance development has also been documented. Some authors emphasize that the increased release of FFAs from adipose tissue could be the first step in this cascade process [14]. FFAs in hypertrophic adipocytes activate specific serine-kinases which are responsible for phosphorylation of Insulin Receptor Substrates (IRS) proteins, and this covalent modification reduces insulin receptor signalling [15]. Also, it is known that FFAs are ligands for several cellular receptors that are involved in the cellular immune response [16]. Binding of FFAs to Toll-like receptor 4 (TLR 4) on pro-inflammatory M1 macrophages induces productions of pro-inflammatory adipokines and stimulates inflammation in adipose tissue [17,18]. Insulin-resistant adipocytes release FFAs into the circulation. Normally, FFAs are utilized either for biosynthesis of complex lipid molecules or for oxidation in different tissues. When the capacities of these two metabolic pathways become saturated, the content of FFAs and their metabolic intermediates increase in the cell, leading to ectopic lipid accumulation and insulin resistance development in liver and skeletal muscle [19]. Increased FFAs flux into the hepatocytes alters glucose metabolism, via hepatic insulin resistance development, but also, by insulin-independent mechanism. Intensive FFAs catabolism in liver increases acetyl-CoA, an allosteric activator of pyruvate carboxylase, which stimulates gluconeogenesis. These processes lead to hyperglycemia and consequent hyperinsulinemia [19,20].

2.2. Adipokines

Adipokines have many different metabolic functions and their role in pathophysiological conditions associated with obesity has been the main topic of numerous studies during the last two decades. Special interest has been focused on their inflammatory aspects [21,22].

2.2.1. Pro-inflammatory adipokines and dyslipidemia

The discovery of leptin, the product of obesity (ob) gene, and its role in the regulation of food intake and energy expenditure was the breakpoint of the concept that adipose tissue is an active endocrine organ [23]. Association of leptin and insulin resistance was observed in leptin-deficient (*ob*/*ob*) mice and exogenous administration of leptin improved insulin resistance [24]. Leptin and insulin have similar general effects on lipid metabolism (Table 1). It is known that leptin participates in the negative feedback loop that reduces insulin secretion, but it also stimulates glucose turnover which improves insulin sensitivity [21]. Leptin is considered a pro-inflammatory adipokine since it stimulates adipose tissue macrophages to secrete tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), interleukin 12 (IL-12) and potentiates low-grade inflammation in adipose tissue [24]. Despite the fact that leptin exhibits pro-inflammatory effect, currently it has therapeutic application in patients with generalized lipodystrophy [25]. Perry et al. [25] showed that leptin reduced glucose concentrations in rodents with poorly controlled type 1 diabetes, by a suppression of hypothalamic-pituitary-adrenal (HPA) activity and consequent reduction of gluconeogenesis and ketogenesis. This result qualifies leptin as a potential new adjuvant therapy in type 1 diabetes and indicates the need for further investigations.

Resistin is an adipokine primarily secreted by macrophages and monocytes in humans and its role in insulin resistance development is not completely clear. Generally, it is accepted that resistin reduces insulin sensitivity in humans, but the results of numerous studies are not uniform. Clinical studies found no correlations between resistin concentration and indices of insulin resistance or obesity [22]. However, there is no doubt that resistin plays a role as a direct molecular mediator of metabolic dyslipidemia development (Table 1). The role of resistin in inflammation is also well known. Inflammatory cytokines stimulate macrophages to secrete resistin by induction of resistin gene expression, while resistin, in turn, promotes the production of pro-inflammatory cytokines [22].

TNF-α is a multipotent cytokine, involved in all aspects of obesity-induced insulin resistance and dyslipidemia development (Table 1). The main mechanism which connects inflammation, particularly TNF-

Table 1
Relevant adipokines and their effects on lipid metabolism

Adipokine	Mechanisms of action	Effects on lipid metabolism
Pro-inflammatory adipokines		
Leptin [21]	Activation of FFAs oxidation enzymes Decrease of TG storage in non-adipose tissues	Lipolytic effect
Resistin [26]	Activation of microsomal triglyceride transfer protein (MTP) Stimulation of apoB-100 synthesis	Increased VLDL production
	Increase of proprotein convertase subtilisin/kexin type 9 (PCSK9) level	Downregulation of hepatic LDL receptor expression
TNF-α [27]	Phosphorylation and activation of hormone-sensitive lipase (HSL)	Lipolytic effect
IL-6 [30]	Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and activator of the Mitogen-Activated Protein Kinase (MAPK) cascade	Lipolytic effect
IL-1 [31]	Suppresion of lipoprotein lipase (LPL) activity	Hypertriglyceridemia
Anti-inflammatory adipokines		
IL-10 [34]	PPAR-γ-dependent ATP-binding cassette transporter 1 (ABCA1)-mediated cholesterol efflux to apolipoprotein A1	Increased HDL-C concentration
Adiponectin [35]	AMPK-activated PPARα transcription factor	Increased FFAs oxidation
Omentin 1 [36]	Activation of AMPK signalling pathway	Inhibition of cholesterol synthesis

α and IL-6, with insulin resistance is a reduced expression of glucose transporter type 4 (GLUT 4) in insulin-dependent tissues under their influence [28]. Also, TNF-α activates serine-kinases responsible for phosphorylation of IRS, specifically Jun N-terminal kinase (JNK) [29]. The specific effect of TNF-α is related to the acceleration of the inflammatory process by induction of synthesis of other pro-inflammatory cytokines, such as IL-6 and IL-1, in the macrophages of adipose tissue. It is also important to note that TNF-α, in cooperation with other inflammatory cytokines (Table 1), induces the activation of the NF-κB pathway and promotes oxidative stress in adipose tissue [32]. Activation of the NF-κB transcription factor by TNF-α is one of the mechanisms which induces inflammation of β-cells and leads to reduced insulin production [33].

2.2.2. Anti-inflammatory adipokines and dyslipidemia

Among anti-inflammatory adipokines (Table 1), adiponectin has the highest concentration in plasma. In adyposopathy, TNF-α, IL-6 and reactive oxygen species downregulate the expression of *ADIPOQ* gene in adipocytes, so the level of adiponectin in the circulation is decreased. The most important mechanisms by which adiponectin enhances insulin sensitivity seems to be via the activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-α (PPAR-α) [35], a transcription factor that regulates lipid metabolism in the liver (Table 1). The main effects are the increased FFAs oxidation and glucose uptake in muscle and the inhibition of hepatic glucose production [37]. Adiponectin also directly influence β-cell function, exerting anti-apoptotic effects [38]. The results of several studies connected adiponectin with the decreased apolipoprotein AI (apoAI) catabolism and higher HDL-C concentrations in plasma [39]. Qiao et al. [40] showed that adiponectin reduces TG concentration in plasma and the underlying mechanism of this effect is the increased activity of LPL, via increased LPL gene expression in skeletal muscle. Adiponectin has also potent anti-inflammatory effects within adipose tissue [41].

Finally, it is interesting to mention specific adipokine Sfrp5, a member of Sfrp inhibitors of wingless-type MMTV integration site family, especially Wnt 5a [42]. Experiments on mouse models proved that Sfrp5 protein is a powerful anti-inflammatory adipokine [43]. Sfrp5 inhibits Wnt 5a-mediated phosphorylation of JNK in adipose tissue and this change in signalling pathway is associated with lower macrophages accumulation in adipose tissue. However, it is not clear whether similar relations exist in humans. The pioneering research of Sfrp5 in humans, concerning its association with the development of insulin resistance gave controversial results, ranging from positive association to no association at all [42,44]. Recently published results of the population-based KORA study showed that Sfrp5 concentration was independently associated with HDL-C, glycated haemoglobin, high sensitivity C-reactive protein and adiponectin concentrations [45]. The observed association between high Sfrp5 and high HDL-C concentrations indicates possible influence of this adipokine on lipid metabolism, but a concrete mechanism is not yet clarified.

2.3. Vitamin D and dyslipidemia in obesity

High prevalence of vitamin D deficiency in obese individuals is well known and confirmed by many investigations. Yet, the exact mechanism which is responsible for this association is still unrevealed. Several hypotheses are proposed and all of them can be classified into three categories. Preliminary theories were based on the associations of vitamin D with anthropometric, physiological and behavioural characteristics of obesity. The ground for second group of hypotheses is the concept which relays on the interplay between dyslipidemia and vitamin D. Finally, the third group of presumptions points towards the crucial role of obesity-related inflammation (Fig. 1). However, a common feature of all above mentioned theories is that vitamin D deficiency is more likely the effect of obesity than its cause. Nevertheless, lack of vitamin D is associated with many unfavourable metabolic aspects of obesity, forming a vicious cycle that finally leads to increased cardiometabolic risk (Fig. 1).

A bulk of evidence suggests that adipose tissue is a direct target for vitamin D actions, in term of modulation of adipogenesis, apoptosis and inflammatory pathways [46–50]. It has been demonstrated that vitamin D exhibits apoptotic effects on adipocytes [51]. Having in mind recent discovery of autonomous bioactivation of this hormone in adipocytes [52], markedly increased amount of vitamin D in adipose tissue may have potential protective effects by preventing hyperplasia of adipocytes. Contrary to studies on mouse cell lines demonstrating inhibitory effects of vitamin D on adipogenesis, Nimitphong et al. [53] showed that vitamin D promotes differentiation of human preadipocytes to mature well-differentiated, insulin-sensitive adipocytes, hypothesizing the role of vitamin D in the healthy remodelling of adipose tissue.

2.3.1. Vitamin D and lipid profile

Up till now, a significant number of observational and interventional studies have been conducted in order to elucidate the interplay between vitamin D deficiency and dyslipidemia, as well as possible therapeutic implications. However, it is still difficult to draw a definitive conclusion regarding the relationship of vitamin D metabolites with serum lipids. A large cross-sectional study by Jorde et al. [54] demonstrated an increase in TC and LDL-C levels across increasing quartiles of 25(OH)D. Conversely, a more recent study by Lupton et al. [55], which included more than 20,000 participants, showed significant associations of vitamin D deficiency with higher concentrations of TC and LDL-C. A Mendelian randomization study by Ooi et al. [56] demonstrated that genetically elevated levels of nonfasting remnant cholesterol are related to decreased vitamin D concentrations, but without

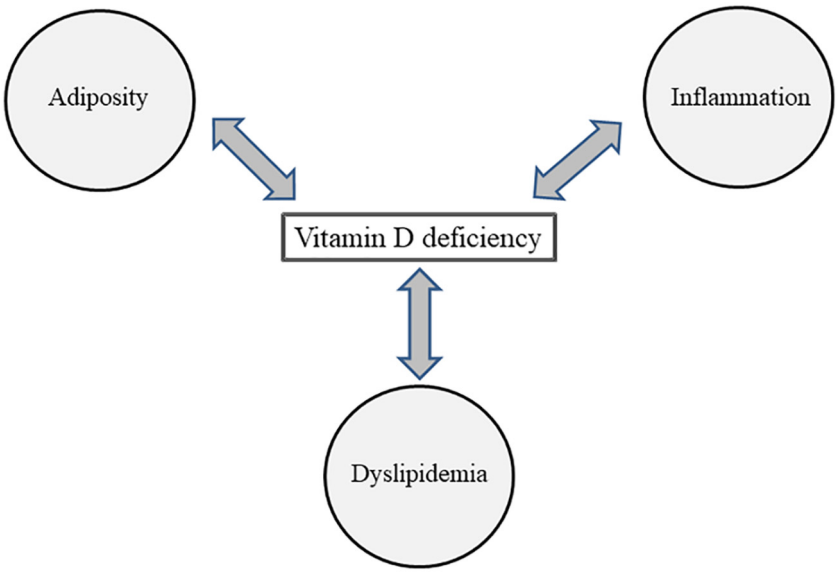

Fig. 1. Possible mechanisms of the associations between obesity and vitamin D deficiency.

evidence for the impact of inherited vitamin D deficiency on cholesterol concentration. Such results suggest that low vitamin D is more likely a marker of dyslipidemia than its contributing factor. The same research [56] demonstrated that genetically low HDL-C levels are associated with higher concentration of 25(OH)D. Similarly, the findings of the Rotterdam study [57] pointed toward inverse and, even more importantly, bidirectional associations between HDL-C and vitamin D plasma levels, suggesting the possible direct impact of vitamin D on HDL metabolism. Finally, previous studies generally pointed toward negative correlations between vitamin D and TG concentrations [58].

Vitamin D and cholesterol share the same biosynthetic pathway since 7-dehydrocholesterol is their joint precursor. Therefore, it has been suggested that the increase in cholesterol biosynthesis would cause a reciprocal decrease in 25(OH)D formation in the skin [57]. Such an assumption can provide an explanation for the previously reported increase in vitamin D level after statin therapy [59,60]. However, not all studies reported such findings and it has been as well demonstrated that statin use does not affect vitamin D levels [61,62]. On the other hand, Chow et al. [63] recently proposed that activation of vitamin D receptor (VDR) both in mice and human hepatocytes leads to enhanced activity of 7α-hydroxylase, which is the rate-limiting enzyme in bile acid synthesis. As a result, parenteral treatment with 1,25(OH)$_2$D caused a decrease of plasma and liver cholesterol in mice [63], suggesting the active role of vitamin D in regulation of cholesterol homeostasis. Finally, one should not neglect the indirect effects of vitamin D, realized through the changes in calcium and parathyroid hormone (PTH) concentrations. Previous researches revealed that higher calcium input increases faecal fat excretion [64], alongside with favourable effects on plasma lipid profile [65,66]. Similarly, sufficient levels of vitamin D are necessary for preventing the development of hyperparathyroidism which is well-known contributor to adverse changes of lipid profile [67,68].

3. Metabolically healthy and metabolically unhealthy obesity — the role of dyslipidemia

Metabolically healthy obesity (MHO) is the term used to designate a subgroup of obese subjects without obvious detrimental consequences of increased weight [69]. In addition, a subset of lean subjects with metabolic disturbances has also been recognized and categorized as metabolically unhealthy normal weight subjects (MUNW) [70]. To date, numerous authors proposed various definitions of MHO, which could be summarised as the absence of the following metabolic disturbances: abdominal obesity, hypertension, dyslipidemia, hyperglycemia and/or insulin resistance. The most common approach to define metabolic health was based on the presence of less than two features of metabolic syndrome [71].

Routine serum lipid parameters are the most frequently evaluated components for distinguishing between MHO and metabolically unhealthy obese (MUO) subjects [72–77]. Albeit obese, MHO subjects are likely to have serum lipid parameters within the recommended range, similarly to metabolically healthy normal weight (MHNW) subjects. In contrast, pro-atherogenic changes are usually found in the lipid profile of MUO and MUNW subjects (Table 2). So far, a limited number of studies have evaluated the lipoprotein subclasses profile, mainly LDL particles, among MHO and MUO individuals. According to available data, MUO subjects have smaller LDL size, increased proportion of sdLDL particles and higher prevalence of LDL B phenotype [76,78,79]. Investigators of Women's Health Study followed 25,626 women for ten years and showed that obese women with dyslipidemia had increased CVD risk compared to obese women without dyslipidemia. The authors did not find the differences in CVD risk between obese and normal weight women without dyslipidemia [72]. Similarly, in the Danish prospective Diet, Cancer and Health study, it was found that obese participants with hypercholesterolemia have a higher risk for the acute cardiovascular event than obese or normal weight subjects without hypercholesterolemia [80].

In recent years more attention has been paid to improve the classification criteria for MHO, in attempt to direct appropriate preventive measures according to the anticipated risk [69,70]. Namely, in the meta-analysis of eight studies Kramer et al. [73] showed that MHO

Table 2
Lipid profile in metabolically healthy and unhealthy obese and normal weight subjects [72–77]

	Metabolically healthy		Metabolically unhealthy	
	Normal weight	Obese	Normal weight	Obese
TC	N	↔	↔	↔
LDL-C	N	↔	↑	↔/↑
HDL-C	N	↔	↓	↓↓
TG	N	↔	↑	↑↑
sdLDL	N	↔	↑	↑

In relation to metabolically healthy normal weight subjects (N, normal): ↔, unchanged; ↑, increased; ↓, reduced. TC; total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C; high-density lipoprotein cholesterol; TG, triglycerides; sdLDL, small, dense LDL.

subjects, when compared to MHNW peers, were not at increased risk of all-cause mortality and/or cardiovascular events. However, MHO was associated with the risk for long-term (≥10 years) adverse outcomes, suggesting the transient nature of this apparently healthy phenotype. More recent meta-analysis of Eckel and co-workers [74] evaluated data from 22 prospective studies and concluded that MHO subjects, regardless of the criteria used to define metabolic health, are at increased risk for cardiovascular events compared to MHNW subjects. Although based on limited data, this study also suggests that MHO might not increase cardiovascular risk for the limited period of time [74]. Thus, the work of both groups led to the same conclusion that MHO confers short-term protection against CVD development [73,74]. Of note, similar observations have been made about the risk for type 2 diabetes mellitus [81,82].

In general, MHO subjects are characterised by less visceral and/or ectopic fat accumulation, as well as by a lower extent of adipocyte dysfunction, as reviewed in detail in [83,84]. Compared to MHO, individuals with MUO have a higher degree of adipose tissue inflammation [71]. Regarding adipokines, results of Framingham Heart Study showed that MHO subjects had lower leptin and adiponectin levels [85]. Other studies found paradoxically higher adiponectin levels in adult MHO subjects [86–88] and adolescent females [89,90]. These data suggest protective role of higher adiponectin levels against obesity-associated metabolic diseases. Studies identified various genes involved in the regulation of adipogenesis and metabolic processes which may predispose to certain obesity pattern [87,91]. The investigations are further extended to epigenetic mechanisms which may be implicated in regulation of obese phenotypes. MicroRNAs (miRNAs) are small, single-strained, non-coding RNAs which regulate protein expression on post-transcriptional level, by blocking mRNA translation or forcing its degradation [92]. Numerous miRNAs are implicated in the regulation of adipogenesis, insulin resistance and inflammation [93,94]. A clear difference in miRNA profile of adipose tissue between lean and obese subjects has been shown [95], as well as in circulating miRNA levels between obese, overweight and control subjects [96,97], suggesting that miRNAs might be explored as biomarkers for distinguishing between MHO and MUO individuals.

4. Novel biomarkers of dyslipidemia in obesity

Over the last decade, the knowledge of the complex link between dyslipidemia and cardiovascular risk has been further expanded with the introduction of novel mechanisms and molecules, constituting potential biomarkers or therapeutic targets. Here, we will discuss obesity-related changes of two recently discovered biomarkers and modulators of LDL metabolism and HDL functionality, i.e. PCSK9 and sphingosine-1-phosphate (S1P), respectively. In addition, functional role of microRNAs and potential use of circulating microRNAs as novel biomarkers of dyslipidemia will be discussed.

4.1. Proprotein convertase subtilisin/kexin type 9 in obesity

PCSK9 is a glycoprotein, predominantly synthesized in hepatocytes, but also in enterocytes, as a zymogen, a preprotein that comprises 692 amino acid residues. It belongs to the proprotein convertase superfamily consisting of nine serine proteases [98]. PCSK9 has no enzymatic activity toward other substrates, except itself, enabling its own secretion in the circulation. However, the catalytic domain of PCSK9 is responsible for its binding to epidermal growth factor (EGF)-A domain of LDL receptor [99]. Following internalisation, PCSK9 impedes recycling of the receptor to the cell surface and enhances its lysosomal degradation (for more comprehensive reviews see [100,101]). There is also another type of interaction between PCSK9 and LDL receptor, which is termed intracellular pathway. In brief, intracellular binding of newly synthesized PCSK9 to LDL receptor fosters degradation of the complex in lysosomes which reduces the level of the receptors at the cell surface [102]. Therefore, the main role of PCSK9 is regulation of LDL receptor levels and, consequently clearance of LDL particles, so as plasma LDL-C level. Recent studies have pointed toward additional mechanisms of interactions between circulating PCSK9, LDL particles and LDL receptors (Fig. 2) including: regulation of both PCSK9 and LDL receptor synthesis via sterol regulatory element-binding protein-2 (SREBP-2) [103], bonding of circulating PCSK9 to LDL particles (approximately 30% of PCSK9) [104] and the impact of PCSK9 on secretion of VLDL particles [100]. The link between PCSK9 and CVD has been confirmed by the results of Mendelian randomization studies, documenting that individuals carrying certain loss-of-function *PCSK9* gene variants have a lower LDL-C level and reduced CVD risk [105]. Accumulating evidence on the role of PCSK9 in dyslipidemia led to the development of novel therapeutic PCSK9 inhibitors with convincing data about their efficiency and safety [106,107].

Available data on the effect of increased body weight on plasma PCSK9 levels and/or association between PCSK9 and obesity indices are scarce and inconclusive. Higher PCSK9 levels were found in obese, as compared to overweight and normal weight subjects [108,109]. Levenson et al. [110] reported that PCSK9 level was higher in obese women and those with type 2 diabetes, but not in obese and diabetic men. In the study of Hasan et al. [111] an inverse association between PCSK9 level and waist circumference in young females was found. In contrast, other groups reported positive correlations of PCSK9 with waist circumference and BMI [112]. As previously explained, insulin resistance and adipokines play major roles in the development of metabolic dyslipidemia. Studies with insulin resistant/deficient mice suggested that insulin enhances hepatic PCSK9 expression [113]. Although studies with animal models demonstrated up-regulation of hepatic PCSK9 expression during hyperinsulinemic-euglycemic clamp [114], clinical studies in healthy subjects and type 2 diabetic patients found no change [115] or even a decrease in plasma PCSK9 levels in obese postmenopausal women [116]. Cariou et al. [117] showed that PCSK9 concentration was positively associated with whole-body and hepatic insulin resistance. In line with the previous findings, large observational studies showed a positive correlation between circulating PCSK9 levels and HOMA-IR in both pediatric [118] and adult [119]

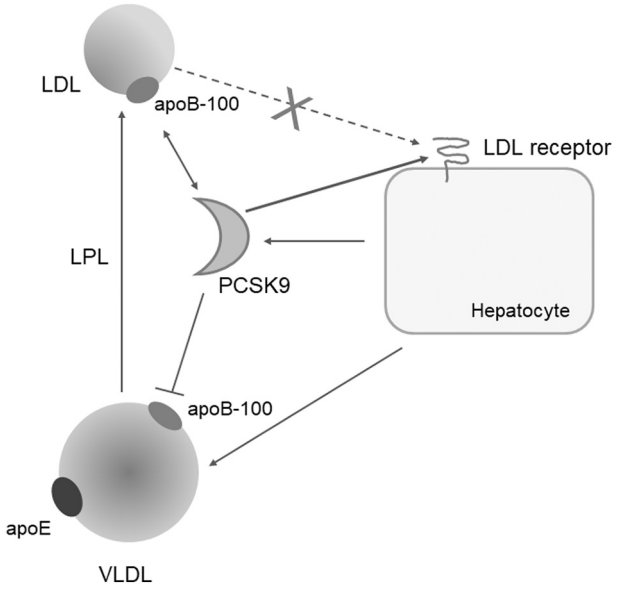

Fig. 2. Mutual relationships between PCSK9, VLDL and LDL particles and LDL receptors. Synthesis of PCSK9 and LDL receptor in the liver is regulated by SREBP-2. The main route of PCSK9 clearance is via LDL receptor. PCSK9 stimulates hepatic secretion of VLDL particles. Hepatic uptake of VLDL remnants following lipolysis in plasma depends on the LDL receptor. Circulating PCSK9 can attach to apoB-100 within LDL particles, but not to apoB-100 within VLDL. Bonding of PCSK9 to LDL particles diminishes its activity toward LDL receptor. PCSK9, proprotein convertase subtilisin/kexin type 9; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; LPL, lipoprotein lipase.

populations. A similarity in the PCSK9 and resistin structures has been revealed by Hampton et al. [120]. It was further demonstrated that resistin reduced LDL receptor, while in turn increased PCSK9 expression in HepG2 cells [121]. Surprisingly, Kwakernaak and colleagues [122] found that plasma PCSK9 level was inversely associated with resistin in lean and insulin sensitive subjects, while in overweight/obese and insulin resistant subjects PCSK9 was not related to resistin at all [122]. Regarding the role of leptin, it has been demonstrated that it suppresses LDL receptor level and LDL uptake but increases PCSK9 expression in HepG2 cells [123]. However, leptin replacement in male *ob*/*ob* mice decreased plasma PCSK9 level but had no effect on lipid parameters. In contrast, upon leptin administration in female mice, plasma lipids were reduced, while the level of PCSK9 remained unchanged [124]. On the other hand, treatment with a synthetic leptin analogue, metreleptin, reduced plasma PCSK9 levels in patients with lipodystrophy [124,125].

One of the mechanisms for a causal relationship between elevated PCSK9 and development of dyslipidemia in obesity is hepatic VLDL overproduction since PCSK9 mediates both apoB-100 and TG synthesis and VLDL assembly pathways [126,127]. In accordance, circulating PCSK9 levels were significantly correlated with serum TG levels in population studies [118,119]. Although there is a rationale for supporting the hypothesis that PCSK9 is involved in HDL metabolism [128], available data showed that PCSK9 is not associated with HDL-C level in obese subjects [110,111,122]. Similarly, little is known about the association between PCSK9 and sdLDL particles in obesity [129]. Several reasons could explain observed unexpected correlations or even lack of associations between plasma PCSK9, obesity indices and lipid profile in clinical and epidemiological studies. It is possible that that the effects observed *in vitro* or in experimental models might not translate into the same associations between plasma lipids and PCSK9 in human studies. Also, conclusions from studies with animal models should be carefully interpreted and translated taking into account the differences in lipoprotein metabolism between the species. Plasma concentration of PCSK9 has very high inter-individual variation [119]. Furthermore, PCSK9 circulates in plasma as intact and as an inactive, furin-cleaved form [130]. As already mentioned, approximately one third of plasma PCSK9 molecules are bound to LDL particles, having diminished activity toward LDL receptors [104]. Thus, it questionable whether plasma PCSK9 level reliable reflects its activity. Available methods do not distinguish between various PCSK9 forms, but measure its total plasma concentration. Development of the tests that quantify PCSK9 forms and/or PCSK9 activity would enable further insight into role of PCSK9 in metabolic dyslipidemia.

4.2. Sphingosine-1-phosphate in obesity

S1P is a member of the sphingolipid family, which comprises a large group of bioactive molecules with a wide range of physiological functions. Sphingolipids are produced in human body either by *de novo* synthesis or by the salvage pathways. S1P in circulation mainly originates from erythrocytes, platelets and endothelial cells [131–133]. The majority of S1P in plasma is bound to HDL particles, and the rest to albumin and other plasma lipoproteins [134]. Physiological effects of S1P are exerted through its interaction with the receptors on target cells, but also through its relationship with its carriers, principally HDL (Fig. 3).

S1P serves as a ligand for 5 different G protein-coupled receptors (S1PR1-5). In general, S1P promotes cell survival, mobility, proliferation, and differentiation, but tissue distribution of the receptors, as well as S1P coupling with specific G proteins ultimately determine its biological effects [136]. In line with this, Hashimoto et al. [137] reported that increased expression of S1P-producing enzyme sphingosine kinase is involved in the promotion of adipogenesis. More recently, it has been demonstrated that S1P stimulates proliferation of adipocytes and adipogenesis [138]. In contrast, Moon et al. [139] reported anti-adipogenic effects of S1P, but these effects are mediated only through S1PR2. Also, it has been demonstrated that the blockade of S1PR2 provokes adipocytes proliferation, but suppresses the differentiation of pre-adipocytes, whereas the opposite is true for S1PR1 [140]. Apart from the receptor-mediated signal pathways, S1P acts as an intracellular signal molecule by mediating TNF-α/NF-κB signalling pathway [141]. Taken altogether, the interplay of receptors' activation and deactivation determines the final effect of S1P, which might provide a ground for the future therapeutic use of S1P analogues.

Approximately two thirds of S1P in circulation is bound to HDL particles. Therefore, the interplay of S1P with serum lipids is predominantly related to the structure and function of HDL. A carrier of S1P within HDL particles is apolipoprotein M (apoM) [142]. This apolipoprotein contributes to atheroprotective effects of HDL by enhancing the cholesterol efflux and antioxidative properties of HDL, but also by serving as a S1P chaperone. Accumulating evidence implicates that atheroprotective actions of HDL strongly depend on the presence of S1P, as well as that the effects of S1P are mediated by its associations with HDL particles. In a recent study, Ruiz et al. [143] have demonstrated that the ability of HDL to act anti-apoptotically depends on the presence of S1P and apoM. On the other hand, anti-apoptotic effects of S1P were more prominent in complex with apoM and HDL, compared to free S1P or its complex with albumin [143]. Similar findings were reported regarding anti-inflammatory and vasodilatatory properties of the S1P [144–146].

It has been demonstrated that obesity influences the entire sphingolipid metabolism. The researchers have found an increased amount of multiple sphingolipids, including S1P in adipocytes of obese individuals [147]. In addition, plasma levels of S1P in obese mice, as well as in obese humans were reported to be elevated [148]. Still, Majumdar et al. [149] found no differences in S1P levels of overweight and lean adolescents. More recent studies shed new light on the relationship between obesity and S1P. Namely, by analysing the liver metabolome, Green et al. [150] demonstrated that calorie restriction causes significant alterations of ceramide and S1P signalling pathways in mice. The authors reported a significantly increased expression of liver S1P, as a response to graded calorie restriction. In addition, S1P negatively correlated with decreasing body mass [150]. Conversely, Silva et al. [151] have found an increase in circulating S1P levels following a high-fat diet in rats. Nonetheless, the same authors [151] demonstrated that a high-fat diet caused a downregulation of hypothalamic S1PR1 protein levels and consequent dysregulation of S1P/S1PR interaction in the neurons of hypothalamus, which is crucial for control of energy balance. Another interesting finding was recently reported by Christoffersen et al. [152]. Namely, the authors showed that apoM$^{-/-}$ mice lacking of S1P signalization have enlarged and hyperactive brown adipose tissue with enhanced TG utilization. Based on these findings, a hypothesis has been raised according to which apoM-S1P complex might have evolutional role in preventing detrimental effects of starvation, but in the condition of food excess, these bioactive molecules might contribute to the obesity development [153].

Green et al. [150] reported negative correlation of liver S1P with circulating leptin levels. Also, it has been shown that leptin resistance in obese rats is associated with increased plasma S1P levels, probably as a compensatory effect [151]. Previously, Holland et al. [154] demonstrated that adiponectin stimulates production of S1P, through activation of both adiponectin receptors AdipoR1/2 and subsequent enhancing of ceramidase activity. More recently, Choi et al. [155] confirmed these findings by demonstrating a decrease in ceramide and increase of S1P following administration of an adiponectin receptor agonist. Thus, accumulating evidences suggest an intrinsic connection between adipokines and sphingolipid metabolism, with S1P as one of the prominent features inside of this metabolic loop. It is noteworthy that, in contrast with numerous investigations on cell cultures and animal models, a number of studies analysing S1P plasma levels in obese or overweight human subjects is relatively small. However, it is clear that the affinity of S1P towards different receptors, but also towards different carriers, determines its final effect in the body. HDL, as the main carrier of S1P in plasma, enables beneficiary effects of this signalling molecule.

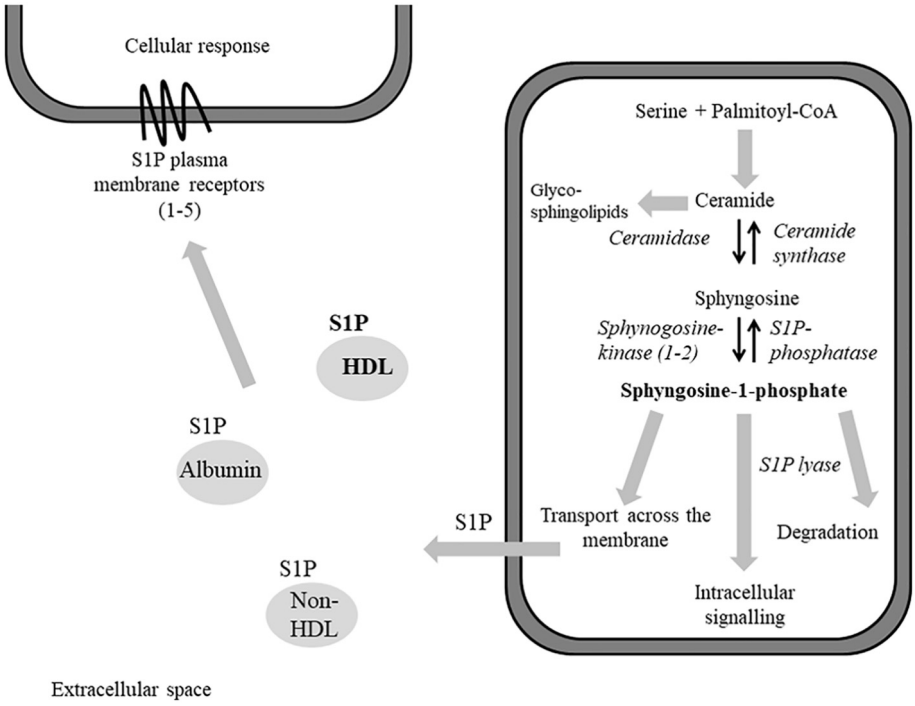

Fig. 3. Metabolism and plasma distribution of S1P. De novo synthesis of S1P starts with a condensation of serine and palmitoyl-CoA and leads to the formation of the major precursor of the entire sphingolipid network: ceramide. Through the activities of several enzymes (sphingomyelin synthase, glucosyl-ceramide synthase or galactosyl-ceramide synthase), ceramide is transformed into sphingomyelin, glucosyl-ceramide, galactosyl-ceramide and further into various glycosphingolipids. In a distinct metabolic pathway ceramide is, by the activities of five different ceramidases, deacylated and transformed into sphingosine. Sphingosine kinases 1 and 2 catalyse the phosphorylation of sphyngosine and formation of S1P. Further metabolism of S1P goes either back to sphingosine throughout the dephosphorisation, or towards an irreversible exit from the sphingolipid metabolism pathway, throughout the cleavage by the activity of S1P lyase [135]. S1P participates in intracellular signalling, or is transported to extracellular space, wherein it bounds to HDL, albumin, or other lipoproteins. Physiological effects of extracellular S1P are accomplished through the associations with membrane S1P receptors (1-5). S1P, sphingosine-1-phosphate; HDL, high-density lipoprotein.

In addition, one should not neglect that obesity is linked with attenuated HDL production and compromised HDL function. In such conditions, higher proportion on S1P will be attached to alternative chaperones, resulting in attenuated or even reversed effects of S1P. In confirming such hypothesis, recently it was reported that apoM-S1P complex is shifted from dense to light HDL particles in women with type 1 diabetes, whereby such assembly of apoM-S1P and light HDL particles is less efficient in promoting anti-inflammatory activities [156].

4.3. Circulating miRNA as biomarkers of dyslipidemia in obesity

Circulating miRNAs are recently established as biomarkers for several diseases and have been repeatedly studied in the context of CVD pathogenesis [157]. Although studies identified numerous miRNAs with important roles in regulation of lipid metabolism [158], a special emphasis will be placed on mir-33a and mir-33b, since they are involved in the regulation of cholesterol and fatty acid metabolism and insulin signalling, which are the hallmarks of metabolic dyslipidemia.

Due to the presence of mir-33a and mir-33b in the introns of the genes encoding transcription factors SREBP1 and SREBP2, respectively, the induction of SREBPs will also induce microRNAs expression. As a consequence, mir-33a upregulation will increase cholesterol synthesis and uptake (via SREBP1-mediated activation of *HMGCR* and *LDLR* genes), and reduce cholesterol efflux (by targeting *ABCA1* and *ABCG1* genes) and elimination (by targeting *CYP7A1* gene) [158]. Similarly, activation of mir-33b will increase cellular lipids, by targeting the genes controlling fatty acid synthesis and oxidation, and also reduce insulin signal transduction, by suppression of IRS-2 gene expression [159]. While the functional roles of mir-33a and mir-33b have been highly investigated, studies on their circulating levels as potential biomarkers are underway. Martino and colleagues [160] found increased plasma miR-33a and miR-33b levels in hypercholesterolemic children and suggested their use as early biomarkers of disrupted cholesterol homeostasis in childhood. In a recent study, both circulating miR-33a and miR-33b levels were positively associated with the levels of serum TC and LDL-C in type 2 diabetes patients with high CVD risk [161]. Finally, miRNA profile analysis in plasma of CVD patients showed three times higher expression of miRNA-33 than in controls [162].

Bonding to HDL and LDL particles protects circulating miRNAs from degradation by RNAses, while, in turn, miRNA cargo of HDL and LDL particles controls their function [158]. Based on the findings that miRNA profile of HDL in healthy subjects differs from the profile in patients with familiar hypercholesterolemia [163] and acute coronary syndrome [164], a hypothesis of unique HDL-associated miRNA footprint in health and diseases has been raised. Subsequent investigations revealed that miR-223, the most abundant miRNA in HDL, mediates HDL anti-inflammatory function [165]. Of note, LDL particles also carry certain amount of miRNA-223, but its role in LDL metabolism is less understood, as compared to miR-155, the most abundant miRNA in LDL, which has pro-atherogenic properties [166]. Recent studies showed that both circulating miR-223 [167] and miR-155 [168] levels correlate with severity of coronary atherosclerosis. Further improvements of the methods for detection of miRNAs in HDL and LDL particles will enable answering the question whether lipoprotein-associated miRNAs may serve as early and sensitive biomarkers of dyslipidemia [169].

5. Implications for cardiovascular disease prevention

Despite significant preventive and therapeutic efforts, development of CVD remains the principal unfavourable outcome of obesity. With an aim to reduce the overall risk for cardiovascular and other chronic complications, clinical practice guidelines for management of obesity acknowledge that the treatment of co-morbidities should be integral part of the obese patients' care [170]. Specific guidelines for the treatment of dyslipidemia in obesity are recently released by the European Society of Hypertension and European Association for the Study of

Obesity [171]. These guidelines recommend lifestyle modification for weight reduction as the main strategy for the regulation of lipid profile [171]. Although obese patients usually have elevated TG and low HDL-C levels, the primary goal of dyslipidemia management is the reduction of LDL-C levels. Actual European guidelines for management of dyslipidemia recognise patients with metabolic syndrome as high-risk individuals and recommend lipid-lowering therapy for those with elevated LDL-C [172], which is applicable to subjects with MUO [71]. Will the newest American College of Cardiology/American Heart Association (AHA) cholesterol guidelines provide specific recommendations for obese patients remain to be seen upon their release in AHA Scientific Sessions 2018 [173].

Apart from well-known strategies aimed to control traditional lipid parameters, contemporary research revealed a range of new modulators of obesity and dyslipidemia, thus providing possibilities for new approaches in prevention of these conditions and related complications. The recognition of MHO and MUO phenotypes might represent the first step in this direction. It is clear that the maintenance of healthy weight depends on a delicate balance between individual susceptibility and lifestyle habits. Although the recognition of MHO phenotype changed the perspective of cardiometabolic risk in obesity, several prospective studies reported transition from MHO to MUO phenotype during follow-up [71,77]. This finding completely fits the conclusion that MHO should be considered as a transient state rather than as a permanent phenotype with low risk [71]. Therefore, additional efforts should be conferred to maintaining MHO phenotype by dietary interventions and overall changes of lifestyle.

An emerging topic of modern scientific investigations is whether novel markers of dyslipidemia are also susceptible to non-pharmacological interventions. To date, several studies have investigated the effects of weight loss on plasma PCSK9 levels in obese subjects. In the study of Filippatos et al. [109] no significant change of PCSK9 level was found after three months of the low-fat dietary intervention program, despite significant weight loss. Similarly, a one-year lifestyle modification program in the study of 117 abdominally obese men showed modest effects on plasma PCSK9 level reduction [129]. Dietary patterns and interventions have different effects on plasma PCSK9 level: it was unchanged following short-term high-fat or high-fat/high-protein diet, increased after high-fructose diet [117] and reduced by Mediterranean diet [174]. As it has been mentioned above, dietary restrictions can increase levels of S1P and expression of S1P receptors [150]. Since S1P associated with HDL particles exhibits significant anti-atherogenic properties, elevation of S1P might present another favourable aspect included in atheroprotective actions of restrictive diet and weight loss. It is also interesting to mention possible effects of physical activity on S1P. Namely, it has been demonstrated that physical exercise increases levels of S1P in animal models [151]. In addition, recent investigation demonstrated selective increase of HDL-associated S1P after the endurance training [175]. Such novel findings implicate that well-known atheroprotective modulators, like restrictive diet and exercise, might have additional beneficial effects which offers new possibilities for preventive actions.

Although many pieces of evidence have pointed toward strong associations of vitamin D deficiency with dyslipidemia, the majority of intervention trials failed to prove beneficial effects of vitamin D supplementation [58], so the question of vitamin D treatment in obese individuals and dyslipidemic patients still remains open. Also, it is noteworthy that, to the best of our knowledge, all previous researches focused on quantitative, but not on qualitative changes of serum lipoproteins. Future studies should elucidate whether vitamin D has any effect on quality and functionality of lipoprotein particles.

6. Conclusion

Impaired production of adipokines and chronic low-grade inflammation in adipose tissue form the base for insulin resistance, which is the main driving force in the development of metabolic dyslipidemia in obesity. In addition, numerous epidemiological data linked vitamin D deficiency and metabolic dyslipidemia, although a clear demonstration of causal relationship is still lacking. The concept of MHO has been recently recognised, indicating a transitional state of relative protection against obesity-related metabolic complications. Knowing that dyslipidemia has a polygenic background, which is additionally modified by the interactions with various epigenetic and environmental factors, this phenomenon may have important implication for long-term cardiovascular prevention in MHO and deserves additional attention. Finally, further investigations of novel lipid biomarkers in obesity would potentially yield new therapeutic approaches for controlling metabolic dyslipidemia and cardiometabolic risk in obesity.

Acknowledgment

This work was granted by the Ministry of Education, Science and Technological Development, Republic of Serbia [Project No. 175035] and supported by the COST Action CA16113.

Author contribution

All authors equally contributed to the present work.

Declarations of interest

None.

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