BBA - Molecular and Cell Biology of Lipids 1866 (2021) 158955

Contents lists available at ScienceDirect

BBA - Molecular and Cell Biology of Lipids

journal homepage: www.elsevier.com/locate/bbalip

Review

Sphingolipids in HDL – Potential markers for adaptation to pregnancy?

Patamat Patanapirunhakit [a,b,*,1], Helen Karlsson [c], Monique Mulder [d], Stefan Ljunggren [c], Delyth Graham [b], Dilys Freeman [b]

[a] Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand
[b] Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[c] Occupational and Environmental Medicine Center, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden
[d] Division of Pharmacology, Vascular and Metabolic Diseases, Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands

ARTICLE INFO

Keywords:
High density lipoprotein
Pregnancy
Preeclampsia
Sphingolipid
Sphingosine-1-phosphate
Ceramide
Vascular function

ABSTRACT

Plasma high density lipoprotein (HDL) exhibits many functions that render it an effective endothelial protective agent and may underlie its potential role in protecting the maternal vascular endothelium during pregnancy. In non-pregnant individuals, the HDL lipidome is altered in metabolic disease compared to healthy individuals and is linked to reduced cholesterol efflux, an effect that can be reversed by lifestyle management. Specific sphingolipids such as sphingosine-1-phosphate (S1P) have been shown to mediate the vaso-dilatory effects of plasma HDL via interaction with the endothelial nitric oxide synthase pathway. This review describes the relationship between plasma HDL and vascular function during healthy pregnancy and details how this is lost in preeclampsia, a disorder of pregnancy associated with widespread endothelial dysfunction. Evidence of a role for HDL sphingolipids, in particular S1P and ceramide, in cardiovascular disease and in healthy pregnancy and preeclampsia is discussed. Available data suggest that HDL-S1P and HDL-ceramide can mediate vascular protection in healthy pregnancy but not in preeclampsia. HDL sphingolipids thus are of potential importance in the healthy maternal adaptation to pregnancy.

1. Background

High density lipoprotein (HDL) cholesterol has a well-established inverse association with atherosclerosis. Theoretically, increasing HDL plasma concentrations should lead to less atherosclerosis-related disease. Unfortunately, clinical trials of HDL cholesterol-raising medication repeatedly failed to reduce the risk of atherosclerotic incidence despite elevations in HDL cholesterol concentration [1–3]. As increasing HDL cholesterol concentrations does not diminish the risk of atherosclerotic vascular disease, attention has instead shifted toward HDL composition and functionality.

In pregnancy, there is a physiological metabolic adaptation involving insulin resistance, inflammation and oxidative stress which could cause vascular damage. Surprisingly, pregnant women have enhanced vascular function despite this unfavorable environment. The reasons for this phenomenon still require elucidation. One possible protective factor may be HDL via its vascular protective properties. HDL concentration is increased in healthy pregnant women and its composition might be involved in functionality [4,5]. So far, little is known about alterations of HDL composition and function in healthy pregnancy and preeclampsia. Here we focus on the sphingolipid composition of HDL and the role of sphingolipids in healthy pregnancy and preeclampsia.

2. Protective role of HDL against atherosclerotic vascular disease

HDL particles contain approximately 50% protein and 50% lipid with phospholipid, cholesteryl ester, free cholesterol and sphingolipid as

Abbreviations: CERS, ceramide synthases; CERT, ceramide transfer protein; CETP, cholesteryl ester transfer protein; dNK, decidual natural killer; EVT, extravillous trophoblast; HDL-S1P, S1P in HDL; HDL-ceramide, ceramide in HDL; PON-1, paraoxonase-1; PLTP, phospholipid transfer protein; SR-B1, scavenger receptor class B type 1; S1P1–5, S1P receptors 1–5; SPT, serine palmitoyl transferase; SPHK, sphingosine kinase; SGPP, S1P phosphatase; SGPL, S1P lyase; TNFα, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule-1.

* Corresponding author at: Wolfson Link building, University of Glasgow, Glasgow G12 8QQ, UK.
E-mail addresses: 2343494p@student.gla.ac.uk (P. Patanapirunhakit), helen.m.karlsson@liu.se (H. Karlsson), m.t.mulder@erasmusmc.nl (M. Mulder), stefan.ljunggren@liu.se (S. Ljunggren), delyth.graham@glasgow.ac.uk (D. Graham), dilys.freeman@glasgow.ac.uk (D. Freeman).
[1] Address Lab 535 Wolfson Link building, University of Glasgow, Glasgow G12 8QQ, UK.

https://doi.org/10.1016/j.bbalip.2021.158955
Received 20 January 2021; Received in revised form 20 April 2021; Accepted 22 April 2021
Available online 29 April 2021

the major lipid components. The major protein in HDL is apolipoprotein A-I (apoA-I) which is involved in HDL synthesis and represents 70% of the total protein in mature HDL particles.

HDL has a wide range of functions, all of which could help protect against vascular dysfunction. Firstly, reverse cholesterol transport is a process whereby HDL promotes cholesterol efflux from various cell types. Cholesterol efflux capacity of HDL shows an inverse relationship with both carotid intima-media thickness and the likelihood of angiographic coronary artery disease, independently of the HDL cholesterol level [6]. Removing excess cholesterol from lipid-laden macrophages is a crucial process in HDL-mediated vascular protection.

Secondly, HDL has antioxidant properties whereby it can remove and inactivate lipid peroxides from LDL and cells. A number of HDL-associated components are involved in lipid peroxide inactivation including apoA-I, paraoxonase-1, platelet-activating factor acetylhydrolase and lecithin-cholesterol acyltransferase (reviewed in [7]).

Thirdly, HDL can enhance vascular function by modulating endothelial nitric oxide synthase (eNOS) expression, leading to increased nitric oxide (NO) production and vasodilation [8]. There are several components of HDL known to take part in HDL-induced NO production. ApoA-I in HDL is required for interaction with scavenger receptor class B type 1 (SR-B1) and stimulates eNOS activity [9]. In addition HDL sphingolipids, such as sphingosine-1-phosphate (S1P), can act via the lysophospholipid receptor S1P3 to induce vasodilatory effects [10].

Lastly, HDL is thought to protect against chronic inflammation in atherosclerosis. HDL has been shown to inhibit the expression of monocyte chemoattractant protein, an important pro-inflammatory chemokine in endothelial cells [11]. It can also reduce tumor necrosis factor α (TNFα) -stimulated expression of pro-atherogenic adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), through both scavenger receptor class B type 1 (SR-B1) and S1P receptors [12,13].

A study in patients with metabolic syndrome demonstrated altered HDL lipidome and lower cholesterol efflux capacity compared to a healthy population. Interestingly, management by weight loss and exercise could modify the patients' HDL lipidome toward that of healthy individuals and improve its cholesterol efflux function [14]. These results emphasize the link between HDL composition and function and changes in HDL composition may play a key role in pathological processes.

3. The role of HDL in pregnancy

3.1. Healthy pregnancy

During pregnancy, maternal metabolic adaptation occurs to provide energy and nutrition for fetal development. In early pregnancy, there is normal or slightly enhanced insulin sensitivity, increased maternal fat deposition and lipogenesis. By mid-gestation, there is a switch to a catabolic state where insulin resistance and lipolysis increase to improve availability of glucose and lipids to the fetus. Inflammation, coagulation and oxidative stress are also elevated in the latter half of pregnancy. Despite this unfavorable environment in healthy pregnancy, vascular function appears to be enhanced. Healthy pregnant women have lower systemic vascular resistance due to vasodilation, leading to a gradual decrease in blood pressure until 20 weeks of gestation. After that, blood pressure rises to the pre-pregnant level (reviewed in [4]).

From 10 weeks of pregnancy, HDL continues to rise and reaches its peak concentration (42% increase) at 20 weeks of gestation, followed by a slow fall to a plateau (7% above early pregnant level) after which HDL remains stable until delivery (reviewed in [4]). As mentioned earlier, HDL plays a key role in preventing vascular dysfunction. Thus, HDL may also exert protective effects in healthy pregnancy. Both the quantity and quality of HDL could be involved in this protection.

3.2. Preeclampsia

Preeclampsia is characterized by the new onset of gestational hypertension with proteinuria or end-organ dysfunction. Primarily, clinical manifestations of preeclampsia result from a generalised maternal endothelial dysfunction. The pathogenesis of maternal vascular dysfunction in preeclampsia is still unclear. One possible mechanism is abnormal development of placental vasculature resulting in placental hypoperfusion/ischemia and release of antiangiogenic factors to disturb maternal endothelial function. Other pathways could be via maternal co-morbidities that predispose to vascular insufficiency. However, these mechanisms do not occur in all patients with preeclampsia. Preeclampsia is known as a multi-factorial disorder and has been categorized into two phenotypes: early-onset preeclampsia and late-onset preeclampsia. Early-onset preeclampsia, developing before 34 weeks of gestation, tends to be associated with placental impairment, intrauterine growth restriction, multi-organ dysfunction and detrimental maternal and neonatal outcomes. Whereas late-onset preeclampsia, developing at or after 34 weeks of gestation, is likely to result from maternal underlying disease and leans toward a normal placenta and normal fetal growth (reviewed in [15]).

Similar to healthy pregnant women, HDL plasma concentration in patients with preeclampsia increases during the gestational period when compared to non-pregnant women. However, the increase in HDL levels in preeclampsia is less and HDL is at significantly lower concentrations than in normal pregnancy [16]. Therefore, reduced amounts of HDL which may be dysfunctional occur and could fail to protect maternal endothelial function in preeclampsia.

4. Sphingolipids

Sphingolipids including sphingosine-1-phosphate (S1P) and ceramide are involved in many biological signaling pathways. S1P in HDL particles (HDL-S1P) has significant anti-atherosclerotic properties. The ceramide content in HDL (HDL-ceramide) could also have a role in vascular function. In this section, the evidence for the role of HDL-S1P and HDL-ceramide in cardiovascular disease and in pregnancy is discussed.

4.1. Sphingolipid metabolism

Ceramide can be synthesized through three pathways. First is de novo synthesis. Sphinganine can be esterified by a family of ceramide synthases (CERS) 1–6 to form dihydroceramide and then ceramides of different acyl-chain lengths dependent on the specificities of each CERS. Ceramide can be converted to other complex sphingolipids such as sphingomyelin. Other pathways for generating ceramide are sphingomyelin hydrolysis, by the enzyme sphingomyelinase, and the salvage pathway that allows complex sphingolipids to be converted back into ceramide.

All sphingolipids are eventually catabolized to ceramide which can be converted to sphingosine and sphingosine-1-phosphate (S1P) by the enzymes ceramidase and sphingosine kinase (SPHK) respectively. S1P production is controlled by reversible phosphorylation via S1P phosphatase (SGPP) and irreversible degradation by S1P lyase (SGPL).

4.2. Sphingolipids in HDL

The source of HDL-S1P could be hepatocytes where HDL synthesis mainly occurs and there is research showing that disturbance of lipid handling in the liver can lead to decreased S1P in HDL [17]. Other major sources of S1P that may be acquired during circulation of HDL in the plasma are blood cells and endothelial cells [18–20]. Several transporters are proposed to transfer S1P to HDL, for example, ATP-binding cassette transporter (ABCC1) and spinster homolog 2 (SPNS2). An ABCC1 inhibitor, MK-571, exhibited an inhibitory effect on S1P

transport to HDL in vitro, but there was no difference in S1P transport between *Abcc1*-deficient mice and wildtype controls [21]. Potentially, SPNS2 has shown a role in intracellular S1P export and S1P levels in plasma and HDL profoundly decreased in Spns2−/− mice [22,23]. Therefore, SPNS2 can be considered as the most likely transporter for S1P. In HDL, apolipoprotein M (apoM) is a specific carrier of S1P that can moderate HDL-S1P homeostasis. It can promote S1P efflux from erythrocytes, physically protect S1P from its degrading enzymes and thus increase HDL-S1P levels [21,24].

With respect to ceramide, subspecies of ceramide with fatty acid chain lengths of 24:0, 24:1, 23:0, 22:0 and 16:0 are the major subspecies in HDL [25]. There is no evidence of direct efflux of ceramide from cells to lipoproteins. However, ceramide can be incorporated into newly synthesized very low density lipoprotein (VLDL) and low density lipoprotein (LDL) in the Golgi and secreted within these lipoproteins into plasma [26–28]. Ceramide then could be transferred to nascent HDL from VLDL or LDL remnants in plasma. The proteins thought to transfer ceramides are cholesteryl ester transfer protein (CETP) and PLTP which are involved in the transfer of other sphingolipids between lipoproteins [29] (Fig. 1).

4.3. Role of HDL-sphingolipids in metabolic and cardiovascular disease

4.3.1. S1P

HDL-S1P is well-known for its role in protection against atherosclerosis. HDL-S1P plays a key role in vascular barrier function by maintaining tight junctions between endothelial cells and preventing inflammation-induced vascular leakage [30–32]. HDL-S1P also promotes survival, proliferation and migration of endothelial cells and vascular smooth muscle cells. Lastly, HDL-S1P regulates vascular tone by inducing nitric oxide synthase (eNOS) and production of cyclooxygenase-2 and prostaglandin I_2 (reviewed in [33,34]). HDL-S1P is involved in both vasodilation and vasoconstriction, but the most significant messenger increased by HDL is nitric oxide which leads to

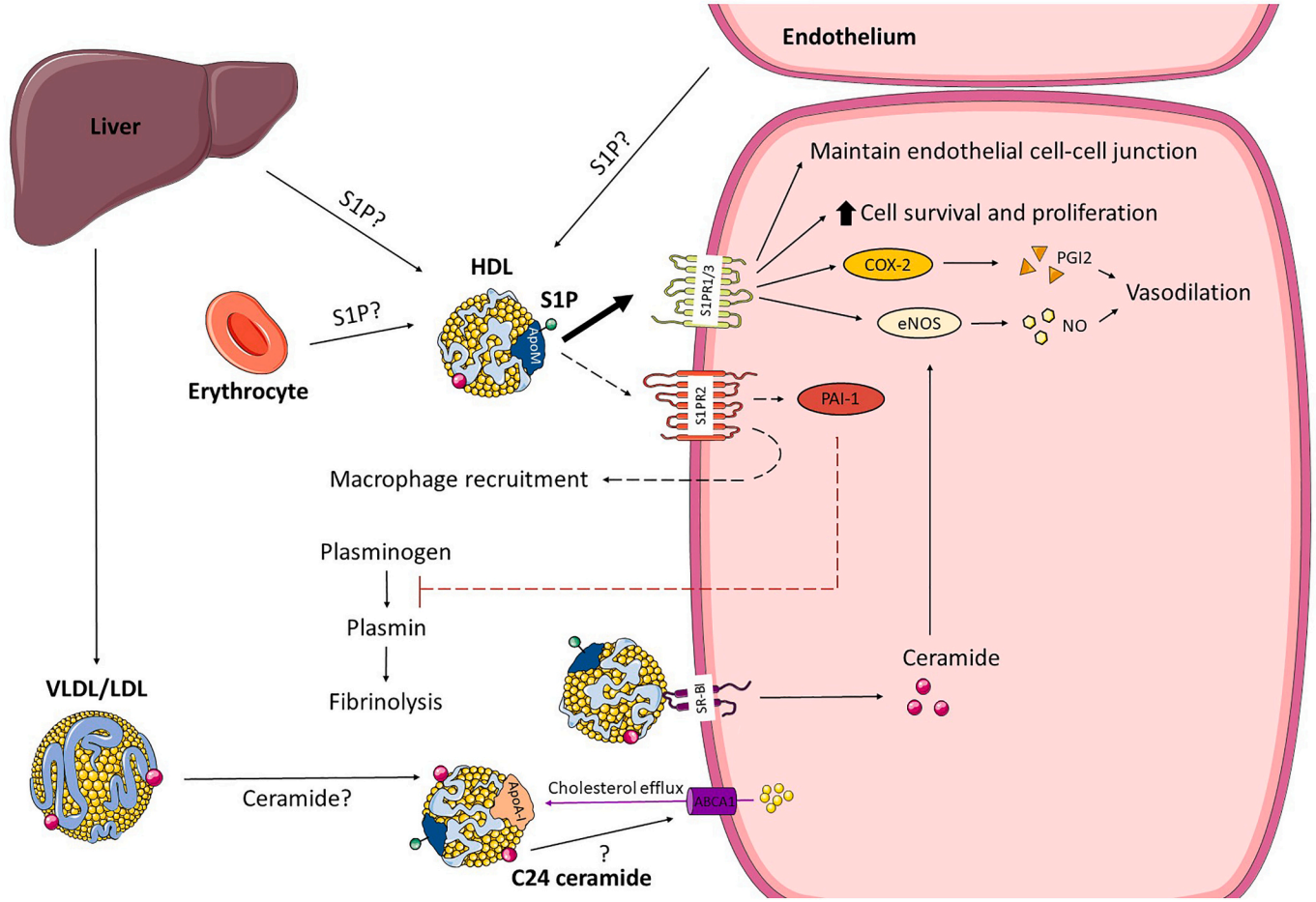

Fig. 1. HDL sphingolipids metabolism and effect on vascular function.
The source of HDL-S1P could be hepatocytes where HDL synthesis mainly occurs or may be acquired during circulation of HDL in the plasma from blood cells and endothelial cells. Ceramide can be incorporated into newly synthesized VLDL and LDL from liver and secreted within these lipoproteins into plasma, ceramide then could be transferred to HDL. HDL-S1P and HDL-ceramide exert their role in vascular protection through various pathways. In HDL particles, ApoM enhances S1P's affinity for the S1PR1 and S1PR3 receptor which predominantly protect endothelial function. S1P-S1PR1 and S1P-S1PR3 signaling help maintain endothelial cell-cell junction, promote cell survival and proliferation, and enhance vasodilation through eNOS and COX-2 stimulation. On the other hand, apoM in HDL weakens S1P's affinity for the S1PR2 receptor, resulting in reduced macrophage recruitment and PAI-1 expression, thus diminished inflammation and thrombosis. Binding of HDL to SR-BI leads to increased intracellular total ceramide level which is involved in the vasodilatory effects of HDL by stimulating eNOS. Ceramide also increases ABCA1 expression which improves cholesterol efflux to HDL. The sources of ceramide in this process could be from HDL particles, especially HDL-C24 ceramide which inversely relate with cardiovascular disease.
HDL-S1P; S1P in HDL, HDL-ceramide; ceramide in HDL, S1P; sphingosine-1-phosphate, VLDL; very low density lipoprotein, LDL; low density lipoprotein, S1PR1–3; S1P receptors 1–3, eNOS; endothelial nitric oxide synthase, NO; nitric oxide, COX-2; cyclooxygenase-2, PGI2; prostaglandin I2, PAI-1; plasminogen activator inhibitor-1, SR-BI; scavenger receptor class B type I, ABCA1; ATP Binding Cassette transporter Subfamily A Member 1, apoM; apolipoprotein M, apoA-I; apolipoprotein A-I.

vasodilation. Impaired HDL-induced eNOS activity has been found in metabolic syndrome patients [35]. This impairment was explained by reduced S1P content in HDL and was normalized by S1P enrichment of HDL [35].

In the pathogenesis of atherosclerosis, circulating S1P acts as an extracellular ligand for S1P receptors (S1PR1–5) which exert a variety of effects. S1PR1 and S1PR3 receptors predominantly exert anti-atherosclerotic actions, whereas S1PR2 exerts pro-atherosclerotic effects. S1PR2 signaling augments plasminogen activator inhibitor-1 (PAI-1) expression which lead to thrombosis and also induces macrophage recruitment and inflammation [36,37]. Meanwhile, HDL-S1P has a distinct role in protecting against atherosclerosis as described earlier. ApoM can be a vital player in this protective role. ApoM seems to enhance S1P's affinity for the S1PR1 receptor while weakening its affinity for the S1PR2 receptor (reviewed in [38]). Thus, ApoM drives HDL-S1P action toward the anti-atherosclerosis pathway (Fig. 1)

4.3.2. Ceramide

Ceramide has different effects on metabolic and cardiovascular disease depending whether it is carried by HDL or not. In tissues, ceramide appears to be involved in inflammation, insulin resistance and impaired vascular function, which can lead to metabolic and cardiovascular disorders (reviewed in [39,40]). Similarly, elevated plasma ceramide levels were found in poor cardiorespiratory fitness and type 2 diabetes and also show a strong relationship with cardiovascular death [41]. However, HDL-ceramide seems to have the opposite properties toward metabolic and cardiovascular disease. Studies in LDL- and VLDL-depleted, HDL-containing fractions of serum exhibited an inverse relationship between C24:1 ceramide level and the incidence of ischemic heart disease [42]. Additionally, sphingolipidome analysis of HDL in type 1 diabetes patients showed a lower proportion of total ceramide on the surface of HDL [43]. A decreased HDL-ceramide level is associated with metabolic and cardiovascular disease. However, further investigation is needed to confirm the role of ceramide in HDL.

Regarding its contribution to the protective roles of HDL, ceramide appears to enhance the anti-atherogenic function of HDL. Several studies indicated that ceramide treatment increases ATP-binding cassette transporter expression which increases binding of ApoA-I to cells and improves cholesterol efflux to ApoA-I [44,45]. Furthermore, ceramide is involved in the vasodilatory effects of HDL by stimulating eNOS to the same extent as HDL [46]. Binding of HDL to SR-BI can also lead to increased intracellular total ceramide levels, eNOS stimulation and vasodilation [46]. The source of ceramide in this process is still unclear. Ceramide may come from caveolae released by sphingomyelinase activity or be provided directly from HDL particles [46]. If the latter situation is true, HDL ceramide could have a protective effect against cardiovascular disease.

Ceramide functional effects may be heterogeneous due to distinct fatty acid chain lengths defining different functions of ceramide. Much research suggests a reciprocal relationship between long-chain (C16 and C18) and very-long-chain (C24) ceramides. Higher ceramide C16:0 and lower ceramide C24:0 were found in HDL of type 1 diabetes patients

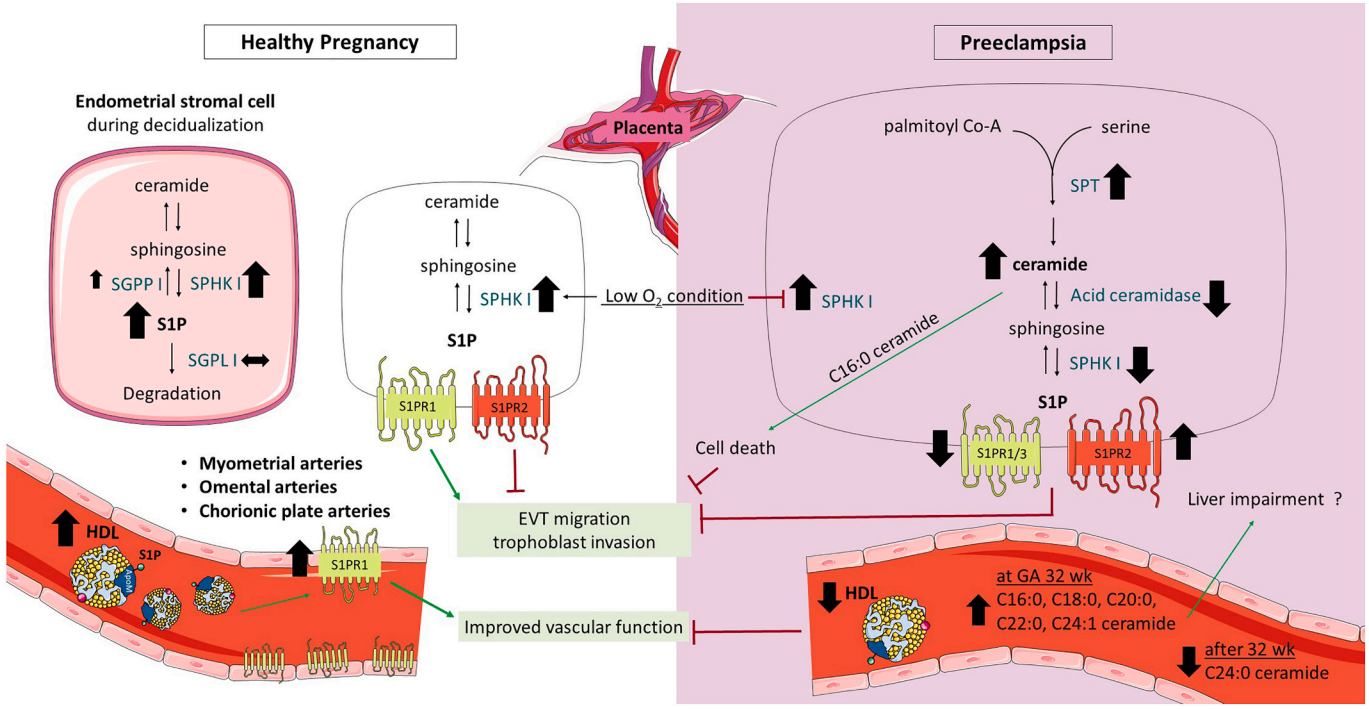

Fig. 2. Sphingolipids and HDL roles in healthy pregnancy and preeclampsia.
S1P and ceramide appear to be crucial in normal pregnancy. After decidualization of endometrium, SPHK I and SGPP I expression were up-regulated, while SGPL I expression was not, suggesting high turnover of S1P and a role for S1P in normal decidualization in pregnancy. Increased plasma HDL and apoM concentration, together with more S1PR1 expression than S1PR2 expression shown in omental arteries, myometrial arteries and chorionic plate arteries, lead to improved maternal vascular function. EVT migration and trophoblast invasion are also enhanced via S1P interaction with S1PR1 in healthy pregnancy, but inhibited by S1P-S1PR2 signaling. Under low oxygen conditions, impaired sensitivity to hypoxia of placenta and an inability to up-regulate SPHKI expression were found in preeclampsia. Also, in preeclampsia, decreased S1PR1 and S1PR3 receptors and increased S1PR2 receptor in placenta suggest impaired EVT migration and trophoblast invasion. The increased de novo synthesis subsequent to SPT activation and decreased breakdown of ceramides via diminished acid ceramidase expression resulting in ceramide accumulation, cell death and impaired trophoblast invasion in preeclampsia. Compared to healthy pregnancy, lower HDL concentration, increased plasma C16:0, C18:0, C20:0, C22:0 and C24:1 ceramide at 32 weeks of gestation, and decreased C24:0 ceramide concentration at 32–36 weeks of gestation in preeclampsia could lead to endothelium and liver impairment.
S1P; sphingosine-1-phosphate, S1PR1–3; S1P receptors 1–3, SPHK I; sphingosine kinase I, SGPP I; S1P phosphatase I, SGPL I; S1P lyase I, apoM; apolipoprotein M, EVT; extravillous trophoblast, SPT; serine-palmitoyltransferase.

[43]. Similarly, plasma ceramide C16:0 and C24:0 ratio strongly relate to cardiovascular events [41]. A study in a mouse model of atherosclerosis and non-alcoholic fatty liver disease also found increased hepatic levels of ceramide C16:0 and C18:0 and decreased C24:0. Inhibition of ceramide synthesis normalized hepatic ceramide levels (reduced long-chain ceramides and increased very-long-chain ceramide), and decreased atherosclerosis and hepatic steatosis [47]. Consistently, experiments in *CERS2* heterozygous transgenic mice, which have reduced very-long-chain ceramide synthesis, reveal compensatory increases in long-chain ceramide leading to susceptibility to insulin resistance and dysregulated lipid metabolism [48]. Therefore, a balance between long-chain and very-long-chain ceramides may play a crucial role in metabolic and cardiovascular disease (Fig. 1).

4.4. Role of sphingolipids in healthy pregnancy

Sphingolipid metabolism has unique characteristics in pregnancy. Serine-palmitoyltransferase (SPT), the rate-limiting enzyme in the de novo synthesis pathway, has three subunits, SPTLC1, 2 and 3. Distinct from other subunits, STPLC3 expression is strikingly high in placenta and it enables generation of the uncommon C16 sphingoid backbone and a special methylated C18-based sphingolipid which are both present in the HDL fraction [49–51]. This raises the possibility that these unique sphingolipids in HDL could contribute to its improved function in pregnancy. However, the physiological role of these sphingolipids in HDL and also in pregnancy is still unclear. Undeniably, while there are some data on plasma sphingolipids, there is limited research regarding the role of HDL-sphingolipids in the metabolism and vascular function of pregnancy. Nevertheless, studies of S1P and ceramide in other aspects of reproduction, as described below, provide potentially relevant information (Fig. 2).

4.4.1. S1P

S1P appears to be crucial in the development of endometrial and placental tissue during pregnancy. In the early stages of pregnancy, proliferative human endometrial stromal cells show high expression of enzymes involved in S1P metabolism including sphingosine kinase I (SPHK I), S1P phosphatase I (SGPP I) and S1P lyase I (SGPL I) [52]. After decidualization, SPHK I and SGPP I expression were up-regulated, while SGPL I expression was not, suggesting high turnover of S1P [52]. Protein expression and activity of SPHK I in decidua increased as gestational age increased [53]. High SPHK activity and high turnover of S1P suggest that S1P might be important in normal decidualization in pregnancy.

After implantation, trophoblast development and invasion take place to drive placental formation. S1P was shown to inhibit cytotrophoblast differentiation during trophoblast development [54,55]. However, S1P effects on trophoblast invasion are heterogenous depending on which S1P receptor S1P interacts with. S1P promotes extravillous trophoblast (EVT) migration via interaction with S1PR1 receptors on EVT, while it inhibits EVT migration via S1PR2 receptors [56,57]. S1P also affects human decidual natural killer (dNK) cell function involved in trophoblast invasion and spiral artery remodeling [58]. Modulation of the S1P pathway can down-regulate S1PR5 receptor expression on dNK cells and impair dNK-mediated EVT migration and endothelial angiogenesis [58]. Thus, the activity of the S1P synthetic pathway could be involved in EVT migration and spiral artery remodeling during pregnancy.

At term, the type of S1P receptors expressed on arteries suggests a role for HDL-S1P in pregnancy. S1P effects on atherosclerosis depend on the type of S1P receptor and HDL-S1P appears to enhance agonist properties on S1PR1 (the anti-atherosclerotic receptor) [38]. There are several types of arteries from healthy pregnant women that show more S1PR1 expression than S1PR2 (pro-atherosclerotic receptor) expression including omental arteries, which represent the maternal systemic vasculature; myometrial arteries, which give a focus on uterine vascular function; and chorionic plate arteries, which affect the fetal-placental circulation [59,60]. These findings support the idea that HDL-S1P may protect vascular function in both the maternal and placental circulation in pregnancy.

Plasma apoM concentration significantly increases throughout pregnancy and reaches peak concentration in the postpartum period [61]. This pattern parallels that of HDL concentration which increases during pregnancy and remains stable in third trimester until around 10 weeks after delivery [4]. These data suggest that the apoM as well as the S1P content of HDL is increased in pregnancy and may lead to enhanced HDL function in pregnancy. Although there was no difference in plasma apoM concentration among healthy pregnancy and other complicated pregnancies such as preeclampsia, gestational diabetes, recurrent miscarriage and small-for-gestational age babies, the link between apoM production and maturity onset diabetes of the young type 3 (MODY3) could provide some hint of a role for apoM in healthy pregnancy [61]. ApoM synthesis is regulated by the transcription factor HIF-1α as reduced apoM expression was specifically found in HNF1A −/− mice and MODY3 patients (who have mutation in *HNF1A*), but not type 1 diabetes mellitus [62–64]. Interestingly, MODY3 is associated with an increased risk of gestational diabetes mellitus (GDM) and unlike other MODYs, MODY3 does not result in elevation of fetal birthweight [65,66]. These findings suggest a correlation between decreased apoM expression and increased risk of GDM and, thus, a role for apoM in maintaining healthy pregnant metabolic adaptation.

4.4.2. Ceramide

The most abundant ceramide species in healthy pregnant women are C24:0 and C24:1 [67,68]. Plasma C24:0, C18:0 and C16:0 concentrations continuously increased from the 1st trimester to 3rd trimester, whereas C24:1 ceramide does not change throughout pregnancy [68].

Additional data regarding ceramide metabolism in pregnancy come from studies in livestock. Healthy bovine pregnancy has metabolic adaptations similar to pregnant humans (increased insulin resistance and lipolysis). In overweight pregnant cattle, most plasma ceramides are further increased, relative to those with a lean phenotype, during pre- and post-partum [69,70]. Hepatic total ceramide and C24:0 ceramide progressively rose during the late gestational period in overweight cows [70]. There was also a linear relationship between increased plasma fatty acid and increased hepatic lipid accumulation in overweight pregnant cows, indicating improved fatty acid supply for ceramide synthesis in the liver [69,70]. The results of this research support the idea that ceramide may be involved in accelerated insulin resistance in overweight pregnancy due to elevated circulating fatty acids in overweight individuals that enhance ceramide synthesis and accumulation in liver and plasma, leading to hepatic lipid accumulation and insulin resistance.

4.5. Role of sphingolipids in preeclampsia

4.5.1. S1P

The S1P pathway appears to be involved in the placental dysfunction of preeclampsia. In normotensive patients, exposure of human placental chorionic villous explants to low oxygen content increased SPHK I mRNA and protein levels [71]. However, reduction of placental SPHK1 gene expression and protein were found in patients with preeclampsia [71]. These finding suggest impaired sensitivity to hypoxia of placenta in pre-eclampsia and an inability to up-regulate SPHK I expression. Also, down-regulated mRNA expression of angiogenic S1P receptors (S1PR1 and S1PR3) in placenta and up-regulated mRNA expression of anti-angiogenic S1P receptors (S1PR2) in chorionic villi were observed in preeclampsia [71]. Thus, an altered S1P/S1P receptor interaction may have an important role in the aberrant angiogenesis observed during placentation in preeclampsia.

Studies on levels of plasma S1P in preeclampsia relative to those in healthy pregnancy are inconsistent. A study in patients with mild pre-eclampsia shows increased plasma S1P concentrations, while another study focused on early-onset preeclampsia revealed decreased serum

S1P concentrations [72,73]. This could be due to differences in S1P levels between serum and plasma or due to the severity of preeclampsia [67]. Nevertheless, in the same group of patients with preeclampsia whose serum S1P was lower than in healthy controls, higher C16, C18, C20 and C24 ceramide concentrations were found in both serum and placental tissue [73]. These data point to a possible role of S1P-ceramide imbalance in preeclampsia (Fig. 2).

4.5.2. Ceramide

There is evidence that disruption of ceramide metabolism is involved in placental impairment and cell death in early-onset preeclampsia. In placenta, higher ceramide accumulation occurs in early-onset preeclampsia compared to healthy pregnancy. Imaging and immunofluorescent staining of placenta also demonstrated higher C16:0 and C24:0 in trophoblast layers and syncytial knots from placenta in preeclampsia. The increased ceramides were the result of increased de novo synthesis subsequent to SPT activation and decreased breakdown of ceramides to sphingosine in lysosomes via diminished ASAH1 (acid ceramidase gene) expression and activity [73]. In the same way, oxidative stress can reduce ASAH1 expression resulting in C16:0 and C18:0 ceramide accumulation [73]. Additionally, C16:0 ceramide was shown to trigger apoptosis, autophagy and necroptosis in trophoblast cells [73,74]. Necroptosis can interfere with the normal process of trophoblast cell fusion which may contribute to aberrant trophoblast invasion [74]. Thus, elevated de novo synthesis together with oxidative stress-induced reduction of lysosomal breakdown favors ceramide accumulation, leading to placental dysfunction and cell death in preeclampsia.

Compared to healthy pregnancy, increased plasma C16:0, C18:0, C18:1, C20:0, C22:0 and C24:1 ceramide were found in preeclampsia at around 32 weeks of gestation [72,73]. Because syncytial knots normally shed into the maternal circulation, increased ceramide accumulation in syncytial knots could be the origin of elevated plasma ceramide concentration in early-onset preeclampsia. Plasma C24:0 ceramide concentration declined at 32–36 weeks of gestation in preeclampsia compared to healthy pregnancy [68]. As mentioned earlier, decreased circulating C24:0 ceramide is associated with liver cirrhosis and cardiovascular disease, thus reduced C24:0 ceramide found in 3rd trimester of preeclampsia may correlate with liver impairment and cardiovascular complications in preeclampsia [41,75] Fig. 2.

5. Conclusion

To provide an appropriate nutrient environment for the fetus, healthy pregnant women adapt their metabolism leading to insulin resistance, lipolysis and inflammation. Although this adaptation could be harmful for vessels, pregnant women surprisingly have enhanced vascular function. Evidence supports a possible role for HDL in exerting protective properties in healthy pregnancy and these may fail to occur in preeclampsia, leading to vascular dysfunction. S1P and ceramide show significant effects in healthy pregnancy and preeclampsia. However, focusing on HDL composition and functionality, there are few data available on the role of HDL-S1P and HDL-ceramide during pregnancy. Such data as there are suggest potential roles for HDL-S1P and HDL-ceramide mediating vascular protection in healthy pregnancy and failing in preeclampsia, however further research is needed to add to the limited evidence base.

Funding

We gratefully acknowledge funding from Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand, BHF Centre of Research Excellence, Oxford BHF Centre of Research Excellence, University of Glasgow, College of Medical, Veterinary and Life Sciences (RE/13/5/30177) and University of Glasgow, College of Medical, Veterinary and Life Sciences and NHSGGC Endowment Project (Ref: GN17OG441). Figures created using images from Servier Medical Art (https://smart.servier.com/) under creative commons licence 3.0.

CRediT authorship contribution statement

PP reviewed the literature, wrote the first draft, and created the figure. DF, DG, MM, HK and SL reviewed the literature and the article and edited final draft.

Declaration of competing interest

The authors declare that they have no competing interests.

References

[1] Group, T.H.-T.C, Effects of extended-release niacin with laropiprant in high-risk patients, N. Engl. J. Med. 371 (3) (2014) 203–212.
[2] M. Gomaraschi, et al., Anti-inflammatory and cardioprotective activities of synthetic high-density lipoprotein containing apolipoprotein A-I mimetic peptides, J. Pharmacol. Exp. Ther. 324 (2) (2008) 776–783.
[3] G.G. Schwartz, et al., Effects of dalcetrapib in patients with a recent acute coronary syndrome, N. Engl. J. Med. 367 (22) (2012) 2089–2099.
[4] W.N. Sulaiman, et al., Does high-density lipoprotein protect vascular function in healthy pregnancy? Clin. Sci. (Lond.) 130 (7) (2016) 491–497.
[5] S. Rauschert, et al., Phospholipids in lipoproteins: compositional differences across VLDL, LDL, and HDL in pregnant women, Lipids Health Dis. 18 (1) (2019) 20.
[6] A.V. Khera, et al., Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis, N. Engl. J. Med. 364 (2) (2011) 127–135.
[7] H. Soran, J.D. Schofield, P.N. Durrington, Antioxidant properties of HDL, Front. Pharmacol. 6 (2015) 222.
[8] Jeffrey T. Kuvin, M., Maria E. Rämet, MD, Ayan R. Patel, MD, Natesa G. Pandian, MD, Michael E. Mendelsohn, MD, and M. Richard H. Karas, PhD, A novel mechanism for the beneficial vascular effects of high-density lipoprotein cholesterol: enhanced Vasorelaxation and increased endothelial nitric oxide synthase expression. Am. Heart J., 2002. 144: p. 165–172.
[9] Ivan S. Yuhanna1, Y.Z., Blair E. Cox1, Lisa D. Hahner1, P.L. Sherri Osborne-Lawrence1, Yves L. Marcel5, Richard G.W. Anderson3, and H.H.H.P.W.S. Michael E. Mendelsohn4, High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase. Nat. Med., 2001. 7: p. 853–857.
[10] J.-R. Nofer, et al., HDL induces NO-dependent vasorelaxation via the lysophospholipid receptor S1P3, J. Clin. Investig. 113 (4) (2004) 569–581.
[11] Mahamad Navab, S.S.I., * Susan Y. Hama,* Gregory P. Hough,* Lori A. Ross,* Richard W. Bork,* and J.A.B. Anthony J. Valente, 11 Davis C. Drinkwater,' Hillel Laks,' and Alan M. Fogelman*, Monocyte transmigration induced by modification of low density lipoprotein in cocultures of human aortic wall cells is due to induction of monocyte chemotactic protein 1 synthesis and is abolished by high density lipoprotein. J. Clin. Invest., 1991. 88: p. 2039–2046.
[12] Dale T. Ashby, K.-A.R., Moira A. Clay, Mathew A. Vadas, and P.J.B. Jennifer R. Gamble, Factors influencing the ability of HDL to inhibit expression of vascular cell adhesion molecule-1 in endothelial cells. Arterioscler. Thromb. Vasc. Biol., 1998. 18: p. 1450–1455.
[13] T. Kimura, et al., Role of scavenger receptor class B type I and sphingosine 1-phosphate receptors in high density lipoprotein-induced inhibition of adhesion molecule expression in endothelial cells, J. Biol. Chem. 281 (49) (2006) 37457–37467.
[14] A.A. Khan, et al., Weight loss and exercise alter the high-density lipoprotein lipidome and improve high-density lipoprotein functionality in metabolic syndrome, Arterioscler. Thromb. Vasc. Biol. 38 (2) (2018) 438–447.
[15] Dahlia Raymond, B., MBS,* and Erika Peterson, MD†, A critical review of early-onset and late-onset preeclampsia. Obstet. Gynecol. Surv., 2011. 66: p. 497–506.
[16] L. Belo, et al., Changes in LDL size and HDL concentration in normal and preeclamptic pregnancies, Atherosclerosis 162 (2) (2002) 425–432.
[17] M. Kurano, et al., Modulation of sphingosine 1-phosphate by hepatobiliary cholesterol handling, FASEB J. 34 (11) (2020) 14655–14670.
[18] K. Venkataraman, et al., Vascular endothelium as a contributor of plasma sphingosine 1-phosphate, Circ. Res. 102 (6) (2008) 669–676.
[19] P. Hänel, P. Andréani, M.H. Gräler, Erythrocytes store and release sphingosine 1-phosphate in blood, FASEB J. 21 (4) (2007) 1202–1209.
[20] L. Yang, et al., Metabolism and functional effects of sphingolipids in blood cells, Br. J. Haematol. 107 (2) (1999) 282–293.
[21] P.M. Christensen, et al., Apolipoprotein M mediates sphingosine-1-phosphate efflux from erythrocytes, Sci. Rep. 7 (1) (2017) 14983.
[22] M. Nagahashi, et al., Spns2, a transporter of phosphorylated sphingoid bases, regulates their blood and lymph levels, and the lymphatic network, FASEB J. 27 (3) (2013) 1001–1011.
[23] S. Fukuhara, et al., The sphingosine-1-phosphate transporter Spns2 expressed on endothelial cells regulates lymphocyte trafficking in mice, J. Clin. Invest. 122 (4) (2012) 1416–1426.
[24] M. Kurano, et al., Liver involvement in sphingosine 1-phosphate dynamism revealed by adenoviral hepatic overexpression of apolipoprotein M, Atherosclerosis 229 (1) (2013) 102–109.

[25] P. Wiesner, et al., Lipid profiling of FPLC-separated lipoprotein fractions by electrospray ionization tandem mass spectrometry, J. Lipid Res. 50 (3) (2009) 574–585.
[26] R.A. Memon, et al., Endotoxin and cytokines increase hepatic sphingolipid biosynthesis and produce lipoproteins enriched in ceramides and sphingomyelin, Arterioscler. Thromb. Vasc. Biol. 18 (8) (1998) 1257–1265.
[27] R.A. Memon, et al., Regulation of glycosphingolipid metabolism in liver during the acute phase response, J. Biol. Chem. 274 (28) (1999) 19707–19713.
[28] A.H. Merrill Jr., et al., Sphingolipid biosynthesis de novo by rat hepatocytes in culture. Ceramide and sphingomyelin are associated with, but not required for, very low density lipoprotein secretion, J. Biol. Chem. 270 (23) (1995) 13834–13841.
[29] X.C. Jiang, et al., Targeted mutation of plasma phospholipid transfer protein gene markedly reduces high-density lipoprotein levels, J. Clin. Invest. 103 (6) (1999) 907–914.
[30] C. Christoffersen, et al., Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M, Proc. Natl. Acad. Sci. U. S. A. 108 (23) (2011) 9613–9618.
[31] K.M. Argraves, et al., High density lipoprotein-associated sphingosine 1-phosphate promotes endothelial barrier function, J. Biol. Chem. 283 (36) (2008) 25074–25081.
[32] S.B. Kumaraswamy, et al., Decreased plasma concentrations of apolipoprotein M in sepsis and systemic inflammatory response syndromes, Crit. Care 16 (2) (2012) R60.
[33] D.G. Hemmings, Signal transduction underlying the vascular effects of sphingosine 1-phosphate and sphingosylphosphorylcholine, Naunyn Schmiedeberg's Arch. Pharmacol. 373 (1) (2006) 18–29.
[34] X. Wang, F. Wang, Vascular protection by high-density lipoprotein-associated sphingosine-1-phosphate, J. Geriatr. Cardiol. 14 (11) (2017) 696–702.
[35] D. Denimal, et al., Impairment of the ability of HDL from patients with metabolic syndrome but without diabetes mellitus to activate eNOS: correction by S1P enrichment, Arterioscler. Thromb. Vasc. Biol. 37 (5) (2017) 804–811.
[36] A. Skoura, et al., Sphingosine-1-phosphate receptor-2 function in myeloid cells regulates vascular inflammation and atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 31 (1) (2011) 81–85.
[37] C. Takahashi, et al., Vehicle-dependent effects of sphingosine 1-phosphate on plasminogen activator inhibitor-1 expression, J. Atheroscler. Thromb. 24 (9) (2017) 954–969.
[38] M. Kurano, Y. Yatomi, Sphingosine 1-phosphate and atherosclerosis, J. Atheroscler. Thromb. 25 (1) (2018) 16–26.
[39] B. Chaurasia, S.A. Summers, Ceramides - lipotoxic inducers of metabolic disorders, Trends Endocrinol. Metab. 26 (10) (2015) 538–550.
[40] S. Grosch, S. Schiffmann, G. Geisslinger, Chain length-specific properties of ceramides, Prog. Lipid Res. 51 (1) (2012) 50–62.
[41] R. Laaksonen, et al., Plasma ceramides predict cardiovascular death in patients with stable coronary artery disease and acute coronary syndromes beyond LDL-cholesterol, Eur. Heart J. 37 (25) (2016) 1967–1976.
[42] K.M. Argraves, et al., S1P, dihydro-S1P and C24:1-ceramide levels in the HDL-containing fraction of serum inversely correlate with occurrence of ischemic heart disease, Lipids Health Dis. 10 (2011) 70.
[43] D. Denimal, et al., Significant abnormalities of the HDL phosphosphingolipidome in type 1 diabetes despite normal HDL cholesterol concentration, Atherosclerosis 241 (2) (2015) 752–760.
[44] A.B. Ghering, W.S. Davidson, Ceramide structural features required to stimulate ABCA1-mediated cholesterol efflux to apolipoprotein A-I, J. Lipid Res. 47 (12) (2006) 2781–2788.
[45] S.R. Witting, J.N. Maiorano, W.S. Davidson, Ceramide enhances cholesterol efflux to apolipoprotein A-I by increasing the cell surface presence of ATP-binding cassette transporter A1, J. Biol. Chem. 278 (41) (2003) 40121–40127.
[46] X.A. Li, et al., High density lipoprotein binding to scavenger receptor, class B, type I activates endothelial nitric-oxide synthase in a ceramide-dependent manner, J. Biol. Chem. 277 (13) (2002) 11058–11063.
[47] T. Kasumov, et al., Ceramide as a mediator of non-alcoholic fatty liver disease and associated atherosclerosis, PLoS One 10 (5) (2015), e0126910.
[48] S. Raichur, et al., CerS2 haploinsufficiency inhibits beta-oxidation and confers susceptibility to diet-induced steatohepatitis and insulin resistance, Cell Metab. 20 (4) (2014) 687–695.
[49] T. Hornemann, et al., The SPTLC3 subunit of serine palmitoyltransferase generates short chain sphingoid bases, J. Biol. Chem. 284 (39) (2009) 26322–26330.
[50] M.A. Lone, et al., Subunit composition of the mammalian serine-palmitoyltransferase defines the spectrum of straight and methyl-branched long-chain bases, Proc. Natl. Acad. Sci. U. S. A. 117 (27) (2020) 15591–15598.
[51] T. Hornemann, et al., Cloning and initial characterization of a new subunit for mammalian serine-palmitoyltransferase, J. Biol. Chem. 281 (49) (2006) 37275–37281.
[52] I.S.W. Jan Riezebos, J.T. Vallance Patrick, Endothelin receptors mediating functional responses in human small arteries and veins, Br. J. Pharmacol. 111 (1994) 609–615.
[53] S.S. Ong, et al., No difference in structure between omental small arteries isolated from women with preeclampsia, intrauterine growth restriction, and normal pregnancies, Am. J. Obstet. Gynecol. 187 (3) (2002) 606–610.
[54] R.A. Lars Edvinsson, Duncan Shawb, Ruth Z. Rutledge, Kenneth S. Koblan, Jenny Longmore, Stefanie A. Kanec, Effect of the CGRP receptor antagonist BIBN4096BS in human cerebral, coronary and omental arteries and in SK-N-MC cells, Eur. J. Pharmacol. 434 (2002) 49–53.
[55] L.E. Hoa Ytterberg, Evidence for a cyclic AMP-dependent pathway in angiotensin AT1-receptor activation of human omental arteries, J. Renin-Angiotensin-Aldosterone Syst. 2 (2001) S42–S47.
[56] M. Westwood, et al., Vitamin D attenuates sphingosine-1-phosphate (S1P)-mediated inhibition of extravillous trophoblast migration, Placenta 60 (2017) 1–8.
[57] W. Yang, Q. Li, Z. Pan, Sphingosine-1-phosphate promotes extravillous trophoblast cell invasion by activating MEK/ERK/MMP-2 signaling pathways via S1P/S1PR1 axis activation, PLoS One 9 (9) (2014), e106725.
[58] Janet R. Ashworth, B., BS, A.Y. Warren, MPhil, P.N. Baker, DM, and I.R. Johnson, DM, A comparison of endothelium-dependent relaxation in omental and myometrial resistance arteries in pregnant and nonpregnant women.pdf. Am. J. Obstet. Gynecol., 1996. 175: p. 1307–1312.
[59] N.K. Hudson, et al., Modulation of human arterial tone during pregnancy: the effect of the bioactive metabolite sphingosine-1-phosphate, Biol. Reprod. 77 (1) (2007) 45–52.
[60] D.G. Hemmings, et al., Sphingosine-1-phosphate acts via rho-associated kinase and nitric oxide to regulate human placental vascular tone, Biol. Reprod. 74 (1) (2006) 88–94.
[61] J. Ahnstrom, et al., Plasma levels of apolipoprotein M in normal and complicated pregnancy, Acta Obstet. Gynecol. Scand. 89 (9) (2010) 1214–1217.
[62] S.A. Mughal, et al., Apolipoprotein M can discriminate HNF1A-MODY from type 1 diabetes, Diabet. Med. 30 (2) (2013) 246–250.
[63] K. Balamurugan, et al., Structure-function studies of HNF1A (MODY3) gene mutations in South Indian patients with monogenic diabetes, Clin. Genet. 90 (6) (2016) 486–495.
[64] S. Richter, et al., Regulation of apolipoprotein M gene expression by MODY3 gene hepatocyte nuclear factor-1alpha: haploinsufficiency is associated with reduced serum apolipoprotein M levels, Diabetes 52 (12) (2003) 2989–2995.
[65] S. Beysel, et al., Maternal genetic contribution to pre-pregnancy obesity, gestational weight gain, and gestational diabetes mellitus, Diabetol. Metab. Syndr. 11 (2019) 37.
[66] Y. Yu, et al., Increased mRNA levels of apolipoprotein M and apolipoprotein AI in the placental tissues with fetal macrosomia, Arch. Gynecol. Obstet. 291 (2) (2015) 299–303.
[67] S.M. Hammad, et al., Blood sphingolipidomics in healthy humans: impact of sample collection methodology, J. Lipid Res. 51 (10) (2010) 3074–3087.
[68] A. Dobierzewska, et al., Plasma cross-gestational sphingolipidomic analyses reveal potential first trimester biomarkers of preeclampsia, PLoS One 12 (4) (2017), e0175118.
[69] J.E. Rico, et al., Plasma ceramides are elevated in overweight Holstein dairy cows experiencing greater lipolysis and insulin resistance during the transition from late pregnancy to early lactation, J. Dairy Sci. 98 (11) (2015) 7757–7770.
[70] J.E. Rico, et al., Temporal changes in sphingolipids and systemic insulin sensitivity during the transition from gestation to lactation, PLoS One 12 (5) (2017), e0176787.
[71] A. Dobierzewska, et al., Impairment of angiogenic sphingosine kinase-1/sphingosine-1-phosphate receptors pathway in preeclampsia, PLoS One 11 (6) (2016), e0157221.
[72] K. Charkiewicz, et al., Sphingolipids as a new factor in the pathomechanism of preeclampsia - mass spectrometry analysis, PLoS One 12 (5) (2017), e0177601.
[73] M. Melland-Smith, et al., Disruption of sphingolipid metabolism augments ceramide-induced autophagy in preeclampsia, Autophagy 11 (4) (2015) 653–669.
[74] L.J. Bailey, et al., Augmented trophoblast cell death in preeclampsia can proceed via ceramide-mediated necroptosis, Cell Death Dis. 8 (2) (2017), e2590.
[75] G. Grammatikos, et al., Serum sphingolipid variations associate with hepatic decompensation and survival in patients with cirrhosis, PLoS One 10 (9) (2015) e0138130.