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Mini review

HDL – associated proteins in hypertensive disorders of pregnancy

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Summary. Hypertensive disorders of pregnancy are associated with various complications and long-term health risks for both mother and child. Preeclampsia, a form of hypertensive disorder, is characterized by gestational hypertension and proteinuria. It is a serious condition that can lead to maternal morbidity and fetal mortality, as well as increased risk of cardiovascular disease later in life. The role of high-density lipoproteins (HDL) in hypertensive disorders of pregnancy has also been investigated. HDL contains many different proteins and is known for its anti-atherogenic, anti-inflammatory, and anti-oxidant properties. Because of their beneficial vascular effects, HDL proteins may prevent vascular damage in physiological pregnancy. However, dysfunctional HDL may be associated with vascular damage and hypertension in pregnancy. Further research is needed to elucidate the HDL proteome and its role in these conditions.

Keywords: HDL, HDL protein, hypertensive disorder, preeclampsia, pregnancy.

HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertensive disorders of pregnancy (HDP) encompass several conditions associated with high blood pressure during pregnancy. These disorders include chronic hypertension, gestational hypertension, chronic hypertension with superimposed preeclampsia, and preeclampsia-eclampsia (Kahsay et al. 2018).

Gestational hypertension (GH) refers to the development of hypertension after 20 weeks of gestation, whereas chronic hypertension refers to hypertension that existed before pregnancy (Roberts and Gammill 2005). Preeclampsia (PE), a severe form of hypertension, is diagnosed when GH is associated with new-onset proteinuria (Roberts and Gammill 2005; Opichka et al. 2021). It is important to note that GH can also occur without proteinuria, which is referred to as transient gestational hypertension (Roberts and Gammill 2005).

Epidemiological studies have highlighted the global burden of HDP. It is estimated that up to 10% of pregnancies worldwide are affected by HDP (Braunthal and Brateanu 2019). Classifying HDP into different categories such as GH, PE /eclampsia, chronic hypertension, and chronic hypertension with PE /eclampsia allows for a better understanding of epidemiological trends and the development of targeted interventions (Wang et al. 2021).

Several mechanisms are involved in the pathogenesis

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of PE, including impaired placental development, oxidative stress, inflammation, endothelial dysfunction, and immune system dysregulation. One of the key factors in the pathogenesis of PE is the failure of spiral arterial remodeling in the placenta, leading to placental hypoperfusion and hypoxia. This leads to oxidative stress, which triggers an excessive systemic inflammatory response and endothelial dysfunction, resulting in vasoconstriction and systemic hypertension. These vascular defects may persist into the postpartum period and contribute to the development of cardiovascular disease (Wu et al. 2017; Opichka et al. 2021). Abnormal trophoblast development and impaired invasion of trophoblast cells into maternal spiral arteries have also been suggested as factors in the development of preeclampsia (Huppertz 2018). The complement system, which plays a role in innate immunity and inflammation, has also been implicated in the pathogenesis of PE (Pierik et al. 2020).

HDPs can have significant effects on maternal and fetal health. They are associated with an increased risk of maternal morbidity and mortality (Magro-Malosso et al. 2017). These disorders are also associated with adverse pregnancy outcomes such as preterm birth, small for gestational age infants, and fetal death (Ahmad and Samuelsen 2012; Macdonald-Wallis et al. 2012). In addition, HDPs have been found to increase the risk of pregnancy-related stroke, particularly in women with preexisting stroke risk factors (Leffert et al. 2015).

HIGH–DENSITY LIPOPROTEIN (HDL) PARTICLES – BASIC STRUCTURE

The structure of HDL is a complex system that plays a crucial role in lipid metabolism and is in constant exchange of lipid and protein components with other lipoproteins and tissues. HDL are the smallest and densest lipoprotein particles, composed of a variety of lipids, proteins, and microRNAs that work together to carry out their functions. The core of HDL is composed mainly of cholesterol esters and triglycerides surrounded by a shell of phospholipids, free cholesterol, and proteins. The proteins contain a hydrophobic portion, with which they are bound to the lipids, and a hydrophilic portion, which faces the aqueous environment/plasma and allows them to be soluble in water (Rohatgi et al. 2021).

In addition to non-esterified and esterified cholesterol and triglycerides, HDL particles contain molecules of phosphatidylcholine, plasmalogen, sphingomyelin, and sphingosine-1-phosphate (S1P). These components are involved in the structural stability of the particle and cholesterol efflux and are substrates for the synthesis of biologically active lipids, etc (Rohatgi et al. 2021).

The major protein of HDL is apolipoprotein A-I (apoA-I), which accounts for about 70% of the protein content of the particle. Other important proteins are apoA- II, apoA- IV, apo C-I, apoC- II, apoC- III, apoE, apoM. Lecithin cholesterol acyltransferase (LCAT), cholesterol ester transfer protein (CETP), phospholipid ester transfer protein (PLTP), and paraoxonase 1 (PON1) also play important roles in HDL function. As part of its "cargo," HDL also carries proteins involved in proteolysis (α-antitrypsin), hemostasis (α-2- HS -glycoprotein), immune response (serum amyloid A – (SAA)), complement activation (complement C3) and inflammation (haptoglobin-related protein) (März et al. 2017; Rohatgi et al. 2021). HDL also contains microRNA molecules. The most abundant is miR-223, which participates in regulating the expression of adhesion molecules on endothelial cells and cholesterol metabolism in the liver (Rohatgi et al. 2021).

The structure of HDL undergoes dynamic changes in response to various physiological and pathological conditions (März et al. 2017; Rohatgi et al. 2021). Lipids and proteins in the structure of HDL are given in Table 1.

HDL PARTICLES – FUNCTIONALITY

HDL fulfills several important functions. One of its main functions is its role in reverse cholesterol transport (RCT), the process by which excess cholesterol is removed from peripheral tissues and transported back to the liver for excretion or reuse (Karathanasis et al. 2017). HDL accomplishes this by interacting with the ATP-binding cassette transporter A1 (ABCA1) and the ABCG1 transporter, which are both responsible for the association of free cholesterol and phospholipids with apoA-I to form nascent HDL particles. ABCA1 is expressed in several tissues, including the liver and intestine (Brunham et al. 2006). LCAT catalyzes the esterification of cholesterol inside the HDL particle, translocating cholesterol to the interior and freeing the shell to accommodate new cholesterol molecules. CETP and PLTP are involved in the exchange of lipid components of HDL with other lipoproteins. In this way, cholesterol is taken up by the liver and excreted unchanged or in the form of bile acids (März et al. 2017; Rohatgi et al. 2021)

HDL is a component of the innate immune response due to its primary anti-inflammatory, cytoprotective, and wound-healing effects. However, HDL particles can have both proinflammatory and anti-inflammatory functions, depending on their structure, macrophage cholesterol content, and signaling pathways. HDL and ApoA-I suppress inflammation by neutralizing bacterial lipopolysaccharide molecules and binding to Toll-like receptors (TLRs) on the surface of macrophages when they block the signaling pathway leading to the synthesis of proinflammatory mediators. The

Table 1. Lipids and proteins in the structure of HDL

Lipids	Cholesteryl esters, Phosphatidylcholine Unesterified cholesterol Triglycerides Sphingomyelins Phosphatidylethanolamine	Plasmalogen Ceramides Oxysterols Bile acids Sphingosine-1-phosphate
Proteins	ApoA-I ApoA-II ApoA-IV ApoC-I ApoC-II ApoC-III ApoD ApoE ApoM Clusterin	PON1 LCAT CETP PLTP ApoL α-antitrypsin α-2- HS –glycoprotein SAA C3 complement Haptoglobin-related protein

Apo – apolipoprotein, PON1 – paraoxonase 1, LCAT – lecithin cholesterol acyltransferase, CETP - cholesterol ester transfer protein, PLTP - phospholipid ester transfer protein, SAA – serum amyloid A.

anti-inflammatory role of HDL is also evident in the suppression of myelopoiesis, monocyte extravasation (by reducing adhesion molecules: monocyte chemoattractant protein - 1, intercellular adhesion molecule - 1, vascular cell adhesion molecule - 1 (VCAM-1), and E-selectin expression (Cockerill et al. 1995; Ashby et al. 1998)) and the differentiation of monocytes into macrophages (März et al. 2017; Rohatgi et al. 2021). HDL may also have anti-inflammatory effects on macrophages by sequestering and reducing the bioavailability of the inflammatory protein SAA in the bloodstream (Kajani et al. 2018). To sequester SAA, ApoA-I must be replaced by it on the HDL surface, causing HDL to lose its anti-inflammatory effect (Tolle et al. 2012).

HDLs can also exert proinflammatory effects by enhancing protein kinase C activation in response to TLR ligands (Van der Vorst et al. 2017). The proinflammatory effects of HDLs are largely due to excessive cellular cholesterol depletion. This activates inositol-requiring enzyme-1α/apoptosis signal-regulating kinase-1/p38 mitogen-activated protein kinase signaling, leading to a proinflammatory endoplasmic reticulum stress response (Fotakis et al. 2019). Under inflammatory conditions, dissociation of ApoA-I from HDL particles occurs, which then directly activates TLRs and further stimulates inflammation (Kajani et al. 2018).

Inhibition of low-density lipoprotein (LDL) oxidation is the main antioxidant effect of HDL. HDL has been reported to act as an antioxidant by scavenging lipid hydroperoxides and detoxifying them into lipid hydroxides, which are further utilised by the liver. Small HDL particles inhibit oxidation more effectively than their large counterparts. PON1 and platelet-activating factor acetylhydrolase (PAF-AH) are two important enzymes in the structure of HDL particles that contribute to their antioxidant effects (Karathanasis et al. 2017; Rohatgi et al. 2021; Zhang et al. 2021). However, the mechanism by which these two enzymes inhibit oxidation is independent of the reduction of lipid hydroperoxides to hydroxides. In this context, PAF-AH hydrolyzes oxidized fatty acids in phospholipids, whereas the mechanism for PON1 is not fully understood (Rohatgi et al. 2021). The possible effects of PON1 are explained in the next section. In addition to apoA-I, which has antioxidant properties (Karathanasis et al. 2017; Zhang et al. 2021), other apolipoproteins associated with HDL, particularly apoE, apoJ, and apoA- IV, also have distinct antioxidant functions (Kajani et al. 2018).

HDL may improve glycemic control by affecting pancreatic β-cells and regulating tissue sensitivity to insulin, thereby exerting an antidiabetogenic role (März et al. 2017; Rohatgi et al. 2021). By increasing the synthesis of the prostacyclin PGI2 and activating nitric oxide synthase (NOS), HDL achieves a vasodilatory effect. By reducing thromboplastin expression and inhibiting factor X, it prevents thrombin formation and blood clotting. HDL also has a stimulatory effect on fibrin degradation (Sulaiman et al. 2016; Kajani et al. 2018).

During pregnancy, there is a physiological metabolic adjustment with insulin resistance, inflammation, and oxidative stress that can lead to vascular damage. Nonetheless, pregnant women have improved vascular function. One possible protective factor could be HDL via the above properties (Woollett et al. 2022).

HDL-ASSOCIATED PROTEINS DURING PREGNANCY AND PREGNANCY COMPLICATIONS

To date, 251 HDL-associated proteins have been validated (Davidson et al. 2022). While some of the references provide insights into lipid profile and HDL function during pregnancy, there are few studies on the HDL proteome in HDP. Some HDL proteins and their significance in normal and pathological pregnancy are presented in Table 2.

Several specific immune system responses are required for healthy pregnancy and delivery – a pro-inflammatory response during implantation and delivery and a more anti-inflammatory response during fetal growth and development. Both immune cells and HDL particles provide proinflammatory and anti-inflammatory status (Rohrer et al. 2006). HDL contains enzymes such as PON1, protease inhibitors (including serine protease inhibitors), and proteins that modify the complement cascade to regulate the pro- and anti-inflammatory state (Girardi et al. 2017; Gordon et al. 2017).

Melchior and colleagues (2021) reported that HDL was enriched in 14 proteins in pregnant women, with the greatest changes found for pregnancy zone protein, angiotensinogen, ceruloplasmin, complement factor B, and alpha-1B-glycoprotein. Conversely, decreases were observed in 11 proteins, with the largest differences occurring in N-acetylmuramoyl-L-alanine amidase, apoA- IV, and albumin (Melchior et al. 2021).

However, differences in the protein composition of HDL, which may be evident in pregnancy complications, may have significant implications for HDL functions. This could have long-term implications for maternal and fetal health (Stadler et al. 2022). Altered HDL metabolism and low HDL levels have been found in hypertensive mothers, and this has been associated with adverse outcomes such as being small for gestational age (SGA) in newborns (Sequeiros et al. 2022).

ApoA-I is a major protein component of HDL particles and plays a crucial role in HDL metabolism and function. ApoA-1 is associated with several physiological processes, including RCT, anti-inflammatory effects, and antioxidant properties (Mains et al. 2011). ApoA-I can increase nitric oxide (NO) production via adenosine monophosphate (AMP)-activated protein kinase (AMPK) signaling thus promoting vasodilation. As mentioned previously, the dissociation of apoA-I from HDL particles occurs under inflammatory conditions (Kajani et al. 2018). Einbinder and coworkers (2018) also showed increased release of apoA-I from HDL particles in women with PE compared with normal pregnancy (Einbinder et al. 2018). In animal models of PE, administration of apoA-I significantly reduced the cytokine-induced increase in systolic blood pressure. In the presence of apoA-I, inflammatory cytokine-induced hypertension in pregnancy and the deleterious effects of TNFα on trophoblast-endothelial cell interaction in humans were suppressed. Gene expression of cell adhesion markers and other molecules involved in trophoblast invasion was decreased (VCAM-1, integrin α6β4, and E-cadherin) (Charlton et al. 2017). The use of apoA-I also reduced pregnancy-associated inflammation (Wu et al. 2019).

S1P is a lipid that is anchored in the HDL particle via apoM and can interact with S1P1 and S1P3 receptors on the vascular endothelial cell, leading to increased endothelial NOS (eNOS) activity, in part via AMPK pathways (Kim et al. 2016; Sulaiman et al. 2016). Another study has also confirmed the role of apoM in regulating endothelial function. The mixture of apoM-S1P or apoM-HDL was able to reduce the presence of adhesion molecules, VCAM-1 and E-selectin, on the cell surface, thereby exerting anti-inflammatory effects. Albumin, which is an alternative S1P carrier, was less efficient than ApoM-bound S1P in inhibiting VCAM-1. Moreover, ApoM-S1P induced the reassortment of S1P-related gene expression to counteract TNF-α (Ruiz et al. 2017). Downregulation of ApoM has been reported in PE and may be involved in impaired placentation (Kim et al. 2016), while increased levels of this apolipoprotein have been found in women with GH (Stadler et al. 2023a). ApoM was also associated with an increased risk of developing GH in these patients [odds ratio (OR) (95% CI (confidence interval)) = 1.64 (1.05-2.57), $P = 0.03$] (Stadler et al. 2023a). In the study by Picot and colleagues (2019), HDL particles from PE pregnant women were shown to lose their antioxidant capacity with decreased levels of S1P and apoM, which could lead to an increase in LDL oxidation and a decrease in NO production (Picot et al. 2019).

PON1 is an enzyme associated with HDL particles and is thought to have antioxidant activity. In addition to its role in preventing LDL oxidation, PON1 may also inhibit the activity of the receptor for oxidized LDL (LOX-1), thereby reducing the production of reactive oxygen species (ROS) via nicotinamide adenine dinucleotide phosphate oxidase and preventing the inhibitory effects of ROS on eNOS (Sulaiman et al. 2016). PON1 is an important determinant of the ability of HDL to stimulate endothelial NO production (Besler et al. 2011). Some studies have found that the ability of HDL to reduce inflammation is diminished as a result of reduced PON1 activity (Uzun et al. 2005). Our study revealed that HDL particles in PE have altered structure and antioxidant capacity. The enzymatic activity of PON1 was higher in the group of women with PE than in the group without PE. This may indicate that pregnant women with PE needed greater antioxidant protection. Although this activity was higher, this increase was not sufficient to protect

Table 2. Overview of some HDL-associated proteins, their reported functions, and observed differences between healthy and pathological pregnancy

HDL- associated protein	Function(s) and/or status in healthy pregnancy	Differences between healthy pregnancy and pregnancy with hypertensive disorder (GH or PE)
ApoA-I	RCT, anti-inflammatory, vasodilatory, antioxidant effects; Reduction of the cytokine-induced increase in systolic blood pressure and decreased pregnancy-associated inflammation; Decreased gene expression of cell adhesion markers - VCAM-1, integrin α6β4 and E-cadherin	Increased release of apoA-I from HDL particles in women with PE compared with normal pregnancy
PON1	Antioxidant activity inhibits the receptor for oxidized LDL, and reduces the production of ROS; Prevents the inhibitory effects of ROS on eNOS, stimulate endothelial NO production	Some studies reported increased PON1 activity in the PE group of women compared with the group without PE, whereas others found decreased PON1 activity; The relative proportion of PON1 activity on HDL3c subclasses was increased in pregnant women with hypertension compared with pregnant women without hypertension. PON1 activity and the relative proportion of PON1 on HDL3c subclasses showed a significant association with hypertension in pregnancy; PON1 activity was higher in early pregnancy with GH than in normotensives and was related to the risk of developing GH
ApoM	Endothelial function - increased eNOS activity; Anti-inflammatory effects - reduce the presence of adhesion molecules, VCAM-1 and E-selectin	Downregulation in PE results in impaired placentation whereas increased levels have been found in women with GH; ApoM has also been associated with an increased risk of developing GH in these patients
ApoC-II, apoC-III, apoA-II, apoE	ApoC-II - cofactor of lipoprotein lipase; apoC-III – inhibitor of lipoprotein lipase; apoA-II – HDL remodeling, cholesterol efflux; apoE – lipoprotein metabolism	No differences in protein abundance were found between healthy and preeclamptic pregnancy
ApoA-IV	Attenuated in healthy pregnancy	/
Alpha-1B-glycoprotein	Enriched HDL in healthy pregnancy	/
Albumin	Attenuated in healthy pregnancy	/
Angiotensinogen	Enriched HDL in healthy pregnancy	/
Ceruloplasmin	Enriched HDL in healthy pregnancy	/
Complement factor B	Enriched HDL in healthy pregnancy	/
N-acetylmuramoyl-L-alanine amidase	Attenuated in healthy pregnancy	/
Pregnancy zone protein	Enriched HDL in healthy pregnancy	/
Protease inhibitors (including serine protease inhibitors)	modify complement cascade to regulate pro- and anti-inflammatory states in pregnancy	/

GH – gestational hypertension, PE – preeclampsia, RCT – reverse cholesterol transport, Apo – apolipoprotein, VCAM-1 – vascular cell adhesion molecule, ROS – reactive oxygen species, NO – nitric oxide, eNOS – endothelial nitric oxide synthase, PON1 – paraoxonase 1

the women from complications (Banjac et al. 2023). Our finding is consistent with that of another research group that also found increased PON1 levels in PE (Agarwal et al. 2012). In another work by our team, the relative proportion of PON1 activity in HDL3c subclasses was increased in hypertensive pregnancies compared with nonhypertensive pregnancies. Moreover, PON1 activity and the relative proportion of PON1 on HDL3c subclasses showed a significant association with hypertension in pregnancy (Ivanišević et al. 2022). However, PON1 gene expression was examined in PE pregnant women, and it was decreased compared with normotensive pregnancies (Arobasalu and Akinlua 2022). In addition, decreased PON1 activity was observed in pregnant women with PE compared with controls (León-Reyes et al. 2017; Einbinder et al. 2018). Systemic oxidative stress with a reduction in PON1 is associated with the severity of PE (Al-Kuraishy et al. 2022). According to Stadler and coworkers (Stadler et al. 2023a), PON1 activity was higher in early pregnancy with GH than in normotensive women and was associated with the risk of developing GH [OR (95% CI) = 1.59 (1.01-2.51), $P = 0.04$]. Another study by the same authors showed no significant changes in PON1 activity between women with PE and women with normal pregnancies (Stadler et al. 2023b). One possible explanation for the contrasting results is that these studies measured activities toward different substrates: arylesterase or lactonase, or that apoB-depleted plasma was used.

The study by Stadler and colleagues (Stadler et al. 2023b) documented the differences in HDL-associated proteins between women with normal pregnancy and those with PE. A higher abundance of apoC-II was found in maternal plasma in both early and late onset of PE than in healthy pregnancy. ApoC-II is a cofactor of lipoprotein lipase and contributes to the hydrolysis of triglycerides. However, no differences in the abundance of apoA-I, apoA-II, apoC-III, and apoE proteins were detected between PE and the control group.

CONCLUSION

Hypertensive disorders are associated with various complications and long-term health risks. Impaired HDL function, altered lipid profiles, and increased risk of cardiovascular disease have been observed in women with HDP. However, the role of HDL-associated proteins in HDP is limited, and the available data provide some insight into their role in maintaining a healthy pregnancy. These findings highlight the importance of considering HDL-associated proteins beyond traditional lipid measurements to understand the role of HDL in HDP. Proteomic analysis has helped uncover the diverse protein composition of HDL particles and their impact on HDL function and disease. Further research is needed to better understand the HDL proteome and its impact on HDP.

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