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Review

VLDL in Atherosclerosis: Variety of Mechanistic Implications

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Abstract: Very-Low-Density Lipoprotein (VLDL) particles play a pivotal role as precursors for Intermediate-Density Lipoprotein (IDL) and eventually transform into Low-Density Lipoprotein (LDL). These particles have been categorized based on size and particle charge. Various types of VLDL impact diverse physiological processes in the human body. The accumulation of VLDL, along with other triglyceride-rich lipoproteins, significantly contributes to the development of atherosclerotic lesions, plaque rupture, progression of liver disorders such as hepatitis and Non-Alcoholic Fatty Liver Disease (NAFLD) and other conditions including obesity, insulin resistance and coronary artery disease. This review delves into the potential of VLDL in averting atherosclerosis and seeks to identify its therapeutic applications. Special emphasis is placed on exploring the role of VLDL in atherosclerosis, understanding its atherogenic properties and utilizing VLDL as a predictive marker for pathological conditions. The study design focuses on examining the data on pathways through which VLDL could be leveraged as a therapeutic target and preventive measure against cardiovascular diseases.

Keywords: Lipids, Atherosclerosis, Cardiovascular Disease, Lipid Metabolism, VLDL

Composition of Very-Low-Density Lipoprotein

VLDL is a lipoprotein that is a precursor of Intermediate-Density Lipoprotein (IDL), which is then transformed into LDL (Feingold, 2022). The standard way of isolating very low-density Lp from plasma or serum is Density-Gradient Ultracentrifugation (DGUC). That is also used to isolate other types of Lp such as LDL, IDL, HDL and Chylomicrons (CMs). The very-low-density Lp lipid core is composed of fatty acids (less than 10%), cholesterol ester (from 10-25%) and triglycerides (from 50-70%) (Chapman *et al*., 1981). ApoB-100 is the main core protein of very low-density Lp. There can be found other proteins such as apolipoprotein E, apoC-1, apoC-2 and apoC-3. These are the surface apoLp that may also regulate lipolysis and function as ligands for membrane receptors (Eric *et al*., 2014).

The Classification of Very-Low-Density Lipoprotein by Particle Size

In the debate surrounding the standard particle diameter for categorizing Very-Low-Density Lipoprotein (VLDL) subfractions, researchers have utilized nuclear Magnetic Resonance Spectrometry (MRS) to determine the size of VLDL particles. To enhance the specificity of this classification, various studies have employed different criteria based on mean diameter values to subcategorize VLDL particles (Mora *et al*., 2009).

In these investigations, reproducibility and accuracy (Holmes *et al*., 2018) have been emphasized to quantify plasma or serum Lipoprotein (Lp) subfractions effectively. Multiple research groups have proposed their own classification systems, leading to differing opinions on the optimal range of standard particle diameters for VLDL subfraction categorization.

For instance, Garvey and colleagues identified three subclasses of VLDL particles based on size: Small (less than 35 nm), medium (35-60 nm) and large (more than 60 nm) VLDLs (Garvey *et al*., 2003). In contrast, Phillips and colleagues proposed a classification scheme with similar subclasses but slightly different size ranges (Phillips and Perry, 2015).

Additionally, Wang and colleagues suggested an alternative approach by delineating VLDL particles into six subclasses based on specific size thresholds, ranging from very small to largest, with the largest subclass involving Chylomicrons (CMs) (Wang *et al*., 2012).

Despite these efforts to refine the categorization of VLDL particles, there remains ongoing debate regarding the ideal standard particle diameter ranges for differentiating VLDL subfractions effectively. This diversity in perspectives underscores the complexity of defining standardized criteria for particle diameter classification in the realm of lipid research.

The Classification of Very-Low-Density Lipoprotein by Particle Charge

Avogaro and colleagues in 1988 were the first to develop a low-density Lp characterization system based on the electrical charge and not on the particle diameter (Avogaro *et al*., 1995). They managed to divide low-density lipoproteins into groups of LDL (+) and LDL (-) through the use of anion exchange (AEX) chromatography. Furthermore, (Chen *et al*., 2022; Yang *et al*., 2005) have identified 5 low-density Lp subclasses (L1-5) based on the surface electrical charge. Chen and colleagues have used the AEX chromatography as well and as a result got 5 subclasses: V1-5.

Hepatic Secretion of VLDL

Consumption of food containing fats, CM is synthesized by the intestine and then interacts with the lipoprotein lipase. As a result, it turns into chylomicron residues which are then absorbed by the liver. Chylomicron residues are an important resource of cholesterol ester and Triglycerides (TGs) (Kenneth and Feingold, 2000). Inside hepatocytes, cholesterol esters and triglycerides are transported to apolipoprotein B 100 in the ER. The very low-density Lp diameter is higher when hepatic triglyceride production is elevated. The lipid composition of very low-density Lp is also influenced by the presence of apolipoprotein B 100 (Heeren and Scheja, 2021). When very-low-density L is secreted into the bloodstream, it reacts with the lipoprotein lipase on the capillary endothelium in a number of tissues, including skeletal, adipose and cardiac muscles. This reaction is followed by the removal of triglycerides from very low-density Lp to be stored or utilized (Pirahanchi *et al*., 2024). One trial demonstrated that in animal models the Intestinal Epithelial Cells (IECs) are able to secrete very low-density Lp which contains apoB-48. Although, this way of secretion of VLDL is yet to be investigated. Imbalance of the normal gut microbiota may be a factor in postprandial dyslipidemia and it also might be connected to aberrant secretion of very-low-density Lp (Yu *et al*., 2019).

Metabolism of VLDL

The summary of normal VLDL function and metabolism is presented in Fig. 1. Very-low-density Lp may be metabolized via hydrolysis by lipoprotein lipase or internalized by the very-low-density Lp receptor. VLDL residue and IDL are formed after VLDL is hydrolyzed by the lipoprotein lipase. ApoC-2 is moved to HDL, which may also exchange Phospholipids (PLs) and triglycerides with cholesterol ester through CEPT (Formanowicz *et al*., 2022). Apolipoprotein E, on the contrary, is obtained by VLDL residue from high-density Lp. The liver is able to recognize about 50% of the intermediate-density Lp using apolipoprotein B 100, the other 50% eventually loses triglycerides and apolipoprotein E and turns into LDL. The liver then absorbs the LDL through the Low-Density Lp Receptor (VLDLR) (Koerner *et al*., 2019). The metabolism of very-low-density Lp may depend on subfractions of apolipoprotein A and apolipoprotein C, Sphingolipids (SL) and other lipid contents e.g., very-low-density Lp is connected to Insulin Resistance (IR) in the presence of apoA2, apoA5, apoC2 and apoC3 (Nishimura *et al*., 2019).

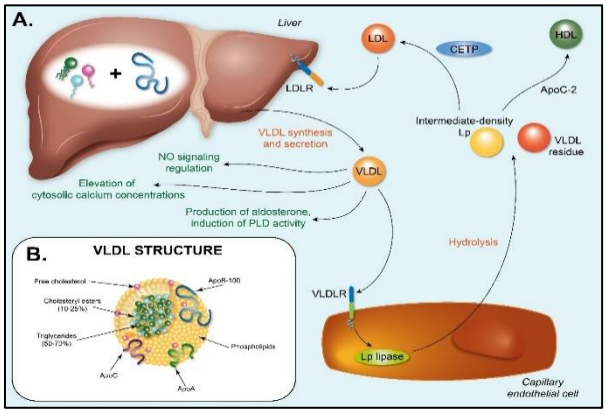

Fig. 1: Structure, function and metabolism of VLDL; (A) Physiologic functions of VLDL; (B) VLDL structure. Abbreviations: ApoA-Apolipoprotein A; ApoB-100-apolipoprotein B-100; ApoC-Apolipoprotein C; CETP-cholesterol ester transfer protein; HDL-high-density lipoprotein; LDLR-Low-Density Lipoprotein Receptor; Lp-Lipoprotein; NO-Nitric Oxide; PLD-Phospholipase D; VLDL-Very-Low-Density Lipoprotein; VLDLR-Very-Low-Density Lipoprotein Receptor

Tissue Expression and Function of VLDL Receptor (VLDLR)

The very low-density Lp receptor is expressed profusely in endothelial cells, lipocytes and cardiomyocytes and is able to take up the VLDL. In peripheral tissues, it can bind the postprandial RLP. Apolipoprotein E may act as the ligand for the very low-density Lp receptor (Chen *et al*., 2021). Thus, the receptor identifies Lp that contain apolipoprotein E, such as very-low-density Lp, very-low-density Lp remnant and intermediate-density Lp. Very-low-density Lp receptor is able to bind to clusterin, reelin and TF Pathway Inhibitors (TFPI) (Basak *et al*., 2012). The interplay of the receptor and lipoprotein lipase has also been observed. VLDL receptor regulates the hydrolysis of triglycerides mediated by low-density Lp. VLDL receptor is a major regulator of lipid metabolism (Krauss *et al*., 2023). Moreover, it was proven to be connected to IR and a number of other pathological conditions, e.g., AD, HTN-CM, AFib and diabetic retinopathy.

The Physiologic Functions of Very-Low-Density Lipoprotein-More than a Cargo Carrier for Lipids

Very-low-density Lp acts as a transporter for protein, cholesterol and triglycerides and transfers them to peripheral blood cells to provide the necessary biological activity. Cholesterol and triglycerides are combined with apolipoprotein B 100 in the liver (Cox *et al*., 1990). This interaction alters the diameter of secreted very low-density Lp and the amount of lipid content. Lipoprotein lipase is found in the capillary endothelial cells or connected to VLDLRs. When the secretion of very-low-density Lp is completed, it undergoes hydrolysis by lipoprotein lipase and then turns into VLDL residue and intermediate-density Lp, from which high-density Lp takes apolipoprotein C-2 (Feingold, 2022). CETP then replaces their phospholipids and triglycerides with cholesterol. The liver may internalize intermediate-density Lp through the low-density Lp receptor or after it is deprived of apolipoprotein E and triglycerides and altered to low-density Lp (Rouland *et al*., 2022). Very-low-density Lp is rich in triglycerides and thus is dependent on IR and prolonged nutrient surplus. Very-low-density Lp also acts as a regulator of NO signaling, which is significantly important for the maintenance of blood pressure and VSM relaxation (Tsai *et al*., 2017). Moreover, very low-density Lp elevates concentrations of cytosolic calcium and promotes the production of aldosterone and thus induces the activity of Phospholipase D (PLD). Thereby, very low-density Lp may also contribute to the regulation of lipid-dependent blood pressure aside from being a transporter (Hattangady *et al*., 2012).

VLDL in CVD

The way that very low-density Lp affects CVD is mostly associated with its influence on AS and CAD. Accumulation of very-low-density Lp, CMs and other Lp rich in TGs promotes the AS plaque ruptures considerably. Furthermore, very low-density Lp is correlated with PAD, which may cause occlusive lesions of the extremities, carotid artery stenosis and vascular stiffening (Muramatsu *et al*., 2019). Not only does the lipid content of very low-density Lp have an impact on CVD progression, but its apoLp content also does. Research demonstrated that elevated levels of apolipoprotein B and decreased levels of apolipoprotein C-3 are correlated with increased CV risk. Therefore, it can be assumed that apolipoprotein B is an important factor in the AS progression (Behbodikhah *et al*., 2021).

Aside from the very-low-density Lp correlation with AS, it also takes part in IR and metabolic syndrome. Normally, insulin inhibits the synthesis and secretion of very low-density lipoprotein. In the presence of insulin resistance, VLDL is produced in excess and its decreased clearance is observed as an elevated concentration of TGs in plasma (Roberts *et al*., 2013). In the case of IR, the accumulation of lipids in body fat does not function properly, leading to an increased risk of hyperlipidemia. In addition, in the case of metabolic syndrome, very low-density Lp may promote the formation of ROS and thus enhance macrophage apoptosis. Due to those cytotoxic features very low-density Lp may contribute to inflammation and AS (Lu *et al*., 2022).

Very-Low-Density Lipoprotein Cholesterol (VLDL-C) is also related to several pathological conditions of the liver, e.g., hepatitis and NAFLD. Earlier, the lipid composition of the liver was believed to be related to other signs of chronic IR, e.g., GI, elevated concentrations of insulin and visceral fat. In patients with non-alcoholic fatty liver disease, very low-density Lp is produced in excess due to enhanced hydrolysis of intrahepatic TGs and its production, oxidation and reduction are changed because of deterioration in insulin function. It was suggested that the weakened action of insulin can induce the deposition of fat in the liver, which can be induced even more by higher levels of glucose in the blood. This may promote the excessive synthesis of VLDL and cause DM-associated hyperlipidemia (Gaggini *et al*., 2013).

Since very low-density Lp metabolism is connected with the endocrine system, its concentrations also depend on a number of hormones. In Cushing syndrome, higher cortisol levels enhance the lipolysis of adipose tissue and decrease the apolipoprotein B degradation, thus elevating the VLDL-C and LDL-C concentrations in plasma, which leads to a higher Cushing syndrome-associated CV risk and dyslipidemia (Kenneth and Feingold, 2020). Very low-density Lp promotes the synthesis of aldosterone, which

may eventually cause hypertension. This sheds light on the link between statins and low levels of aldosterone. Metabolism of very low-density Lp is also dependent on growth hormone. Its diminished secretion is related to elevated production and reduced clearance of VLDL, which accounts for the connection between hypopituitarism and increased risk of cerebrovascular and CV events (Andersson and Vasan, 2015). Furthermore, Triiodothyronine (T3) and Thyroxine (T4) are connected to cholesterol metabolism and have an impact on the lipoprotein lipase function. In the case of hypothyroidism, the deficiency of these hormones may impair lipoprotein lipase activity and elevate VLDL synthesis in the liver, which correlates with increased CV risk and hyperlipidemia. Very low-density Lp is also associated with the progression of cancer, CKD and neurocognitive impairment (Mavromati and Jornayvaz, 2021).

The liver produces VLDL-C to carry TGs and CE to peripheral tissues. It is directly related to the progression of numerous multiorgan disorders, e.g., cancer, AS, CAD, NAFLD, IR, autoimmune disease, metabolic syndrome, neurocognitive disorders and skin disorders. Further research on VLDL is needed to elucidate its nature and role in human health, which would help improve treatment and general healthcare (Heeren and Scheja, 2021).

Potential Contributions of VLDL to Atherogenesis

The variety of potential contributions is depicted in the Fig. 2.

Cholesterols carried by both low-density lipoprotein and very-low-density lipoprotein are associated with atherosclerosis.

Non-AS and AS CVD cannot be predicted only by low-density Lp cholesterol in plasma, since VLDL-C also takes part in the progression of AS cardiovascular disease. Non-high-density Lp cholesterol contains plasma VLDL cholesterol, which may predict AS cardiovascular disease independently of low-density Lp cholesterol (Ali *et al*., 2012).

Prenner and colleagues studied coronary artery calcification using a cardiac EBCT scan (Prenner and Chirinos, 2015). In T2DM patients, coronary artery calcification is an important predictor of cardiovascular risk. The study demonstrated that VLDL cholesterol proved to be an independent coronary artery calcification risk factor, especially in female patients. In addition, concentrations of triglycerides did not affect this association. In T2DM individuals with coronary stents, increased concentration of VLDL cholesterol (more than 0.52 mmoL/L) is independently related to In-Stent Restenosis (ISR), with hazard ratio = 3.01. Iannuzzi and colleagues (Iannuzzi *et al*., 2021) found VLDL cholesterol association with subclinical AS, using ultrasonography to check the thickness of the carotid intima-media complex in female patients of postmenopausal age.

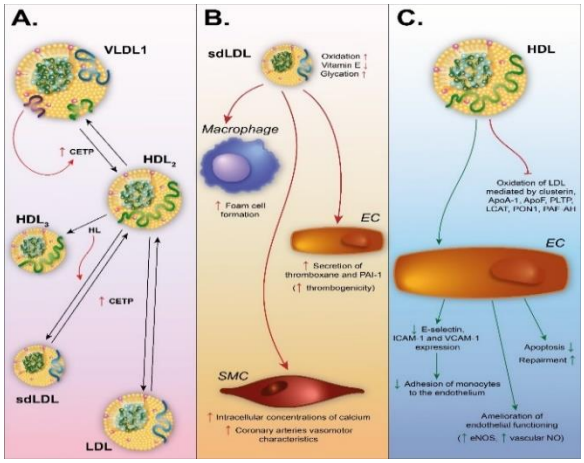

Fig. 2: Diversity of LDL functions in atherogenesis; (A) VLDL promotes pro-atherogenic changes in HDL and LDL; (B) Pro-atherogenic function of sdLDL; (C) Anti-atherogenic function of HDL

Moreover, clinical trials repeatedly showed a causative role of VLDL and other triglyceride-predominant Lp in atherosclerotic cardiovascular disease. Recently, the presently available data on the Lp rich in triglycerides' role in AS cardiovascular diseases was published (Reiner, 2018).

VLDL accumulation promotes pro-atherogenic changes in other plasma lipoproteins High-Density Lipoproteins (HDL) and LDL by accelerating neutral lipid exchange reactions.

There are two categories of very low-density lipoproteins. The first one-VLDL1-includes large particles rich in TGs (diameter from 50-80 nm; 70% TG mass). The second one-VLDL2-includes small and more dense particles (diameter from 30-50 nm; 30% TG mass). T2DM, FCH and other conditions in which VLDL1 is produced in excess in the liver are associated with hypertriglyceridemia, decreased levels of HDL-C and generation of small and dense low-density lipoproteins (Castillo-Núñez *et al*., 2022). In the presence of an increased concentration of newly produced VLDL1, the activity of CETP is enhanced. This mediates the exchange of CE to TGs between HDL2 and VLDL1, which forms TG-rich HDL2 and CE-rich VLDL. TG-rich HDL2 acts as a substrate for Hepatic Lipase (HL). HL is an enzyme that causes lipolysis of TGs and PLs. As a result, TGs and PLs are converted into small and dense High-Density Lp (HDL remnants or HDL3) and low lipid apoA1, which is quickly removed from the bloodstream by kidneys (Chapman *et al*., 2010). This process is directly related to the formation of small and dense low-density Lp. Cholesterol ester transfer protein promotes the TG's transportation from TG-rich Lp to low-density Lp, leading to elevated affinity for HL and hydrolysis of TGs. Low-density Lp formed this way are smaller, more dense and devoid of cholesterol, their plasma half-life is longer and their affinity for subendothelial space is higher

(Westerterp *et al*., 2006). With plasma TG levels higher than 133 mg/dL, the small dense Low-Density Lipoproteins (sdLDL) prevail among all low-density Lp. Basically, VLDL1 rich in TGs storage in plasma may lead to atherosclerotic changes in both low-density and high-density lipoproteins (Ivanova *et al*., 2017).

High-density lipoproteins have a pleiotropic effect, preventing AS. HDLs are able to stimulate the RCT from lipid-rich macrophages to the liver. Then cholesterol is removed from the liver via bile and feces (Ouimet *et al*., 2019). Moreover, high-density lipoproteins reduce the E-selectin, ICAM-1 and VCAM-1 expression, thus reducing inflammation in vascular EC. Adhesion of monocytes to the endothelium is one of the first stages of a process that leads to AS plaque formation. E-selectin, ICAM-1 and VCAM-1 mediate this adhesion (Cook-Mills *et al*., 2011). In addition, high-density Lp may suppress oxidation of low-density Lp, which is mediated by clusterin, apolipoprotein A-1, apolipoprotein F, Phospholipid Transfer Protein (PLTP), LCAT, PON1, PAF-AH. There are several more ways of inhibition of AS development by high-density Lp. HDL is able to protect EC against apoptosis, promote repairment of EC, exert antithrombotic effect by reducing TF expression in EC and ameliorate endothelial functioning by enhancing activation of endothelial NOS, which in turn elevates vascular nitric oxide (Brites *et al*., 2017).

Small and dense low-density Lp has a stronger atherogenic effect compared to large buoyant low-density Lp. Small and dense LDL has lower affinity for the LDL Receptor (LDLR) due to the changes in the apolipoprotein B ligand site conformation and thus their plasma residence time is longer. Consequently, there is a higher probability of transition to the subendothelial space (Borén *et al*., 2020). These particles are able to go through the endothelial barrier because of their smaller diameter (from 1.5-1.9 times more than other low-density Lp). Levels of sialic acid on the surface of the endothelial barrier are reduced. Therefore, the barrier has a higher affinity for arterial intimal matrix Proteoglycans (PGs), which contributes to their deposition in atherosclerotic plaques and subendothelial space. Small and dense LDL susceptibility to oxidative modifications is increased, probably because of their low vitamin E concentration (Cortés *et al*., 2020). SdLDLs also have increased susceptibility to glycation even without the presence of hyperglycemia, probably because of the prolonged residence time or of a higher portion of lysine remnants located on the particle surface. All these alterations elevate the affinity of the particles for the macrophage SRs inside the arterial intima layer (Singh *et al*., 2014). After macrophages are enriched in CE, they turn into foam cells, which is the primary atherosclerotic lesion. In the EC, small and dense LDLs elevate thrombogenicity by promoting thromboxane and PAI-1 secretion (Reiss and Cronstein, 2012). In arterial SMCs, they elevate intracellular concentrations of calcium and thereby enhance the coronary arteries' vasomotor characteristics. Then these particles get saturated with Lp-associated PLA2 and apolipoproteins with atherogenic characteristics (such as apolipoprotein C 3) (Pokharel *et al*., 2015).

The said characteristics of small and dense low-density Lp are of clinical importance. The speed, at which these particles penetrate the vascular wall and stay inside the subendothelial space, mainly depends on the amount of Lp that carries apolipoprotein B. It is easier to enter the arterial wall for the particles depleted in cholesterol than for low-density Lp rich in cholesterol and thus larger in size (Lorey *et al*., 2022). But at the same time, low-density Lp of bigger size are able to inflict more damage to the tissues, since they contain a larger amount of cholesterol and release it in the damaged blood vessel wall. Hereby, atherosclerotic development may be promoted by both large LDL particles and sdLDLs, although, the ways may vary depending on the LDL category. 24 studies have assessed the connection between different subclasses of low-density Lp and CV events (Ishii *et al*., 2022). A review of these studies has drawn a conclusion that the frequency of adverse CV events is mostly dependent on the amount of low-density Lp and not their diameter. The necessity of developing a way to detect small and dense LDL-predominant cases has also been implied. The concentrations of small and dense LDL in plasma turned out to have less effect on the LDL-C levels than previously thought. Small and dense LDL is usually found in individuals with T2DM and metabolic syndrome in the presence of mildly increased TGs. Under these circumstances, LDL-C may not predict atherosclerotic events accurately (Superko and Garrett, 2022). There are other options such as apoB and non-HDL-C levels. The non-HDL-C option suggests that all cholesterol that is not carried by nigh-density Lp has atherogenic characteristics. Measurement of apoB is a better way since it is a marker for various Lp with atherogenic properties. Therefore, in the presence of increased TG-rich Lp levels, the determination of apolipoprotein B and non-HDL-C should be the approach of choice (De Nijs *et al*., 2013).

Plasma Accumulation of other Atherogenic Particles (VLDLs and Remnants) Besides LDLs

Very-low-density Lp and residues have a similar risk of atherogenicity as low-density Lp. Mendelian randomized analysis included 654,783 patients and demonstrated that LDL-cholesterol-decreasing variants of the LDL-receptor and lipoprotein lipase variants related to decreased TGs are associated with equally reduced risk of CAD per each 10 mg/dL reduction in apolipoprotein B, with ratios of 0.773 and 0.771 (Ference *et al*., 2019). The benefit of lowering TG-rich Lp is equal to the benefit of lowering low-density Lp cholesterol, after adjustment per unit of change in concentrations of apolipoprotein B.

Since the plasma half-life of low-density Lp is longer, its amount in plasma is much more than that of TG-rich Lp. In individuals with normal TG concentrations, the ratio of very-low-density Lp and low-density Lp is about one to nine (Enkhmaa *et al*., 2020). When TG levels are elevated in the presence of hypertriglyceridemia, those amounts are considerably closer to each other. In the case of dysbetalipoproteinemia with no medical treatment, the amount of VLDL is much larger than that of LDL (Berglund *et al*., 2012). A report published lately in Denmark demonstrated that the risk of adverse CV events is higher for very-low-density Lp than for low-density Lp, which was estimated from the number of particles registered by nuclear MRS. The hazard ratio for MI was 3.5 times for very-low-density Lp and 1.3 times for intermediate-density and low-density Lp. It was also suggested by the authors that very-low-density Lp and low-density Lp particles should be evaluated separately since the former have higher atherogenicity (The Emerging Risk Factors Collaboration, 2009).

Very-low-density lipoproteins are more atherogenic than low-density lipoproteins and there could be a number of reasons for that. VLDL contains larger amounts of cholesterol than low-density Lp due to its size (Sandesara *et al*., 2019). In the intermediate-density Lp range, a remnant particle can comprise 4 times more cholesterol than a low-density Lp particle (approximately 8600 cholesterol molecules per particle versus 2000-2700 molecules per particle). Moreover, since these particles are rich in apolipoprotein C 3, they can enter the arterial intima layer more easily. C-Reactive Protein (CRP) is an inflammatory marker; its elevated levels are related to TG-rich Lp accumulated in plasma. Thereby, lipoproteins rich in TGs are able to induce AS plaque rupture, inflammation of the arterial intima and myocardial infarction (Ginsberg *et al*., 2021).

Altered low-density Lp are as atherogenic as the VLDL remnants, since to latter are more susceptible to chemical modifications. The LDLs and the remnants have an equal impact on the endothelial and monocyte adhesion molecule expression, as well as on the inflammatory gene expression in vascular EC via a reduction-oxidation-sensitive mechanism (Chen and Khismatullin, 2015). Both these two classes of particles are chemotactic for macrophages, monocytes and T cells. They are also able to promote the transformation of macrophages into foam cells and to reduce the activity of nitric oxide, thus modifying EC relaxation. Oxidized low-density Lp and chemically altered VLDL remnants also have an equal atherogenic impact on ECs and SMCs, including the ability to promote TF expression, contribute to the aggregation of platelets, promote apoptosis and exert cytotoxic effect. Another way by which altered TG-rich Lp, but not low-density Lp, can promote AS is their ability to activate Lectin-like Oxidized LPL receptor 1 (LOX-1) in ECs, leading to impairment of their function (Takahashi *et al*., 2002).

Genetic Variants Associated with Very-Low-Density Lipoprotein Particles

Lp categories are associated with several gene variants. E.g., the common variant rs73059724 led to smaller very-low-density Lp particles with a smaller number of PLs. Variant rs73059724, located on chr19 is linked to the promoter and intron of HIF3A, which stimulates hypoxia and controls the absorption of CEs and very-low-density Lp by cells (Emdin *et al*., 2016). Moreover, HIF3A hypermethylation is linked to a higher obesity rate in Asian neonates and children. These discoveries support the idea that HIF3A controls the size of very low-density Lp particles. Additionally, DNA methylation at the HIF3A gene could shed light on the prenatal impact on obesity. Li-Gao and colleagues conducted research in which they studied postprandial metabolomics. The results indicated that the ANKRD55 locus led by the rs458741: C gene variant had a direct connection with body composition, extralarge very low-density Lp and frequency of DM. These discoveries emphasize the connection between IR and modifying very low-density Lp (Wang *et al*., 2015).

Gut Microbiome Imbalance

A study performed by Vojinovic and colleagues included 2309 patients, the results demonstrated that 32 microbial families and genera in intestinal microbiota are linked to different subclasses of very-low-density Lp, high-density Lp, levels of lipids in serum and metabolites associated with glycolysis, with the subclasses determined by the particle size (Vojinovic *et al*., 2019). 18 of these microbial families and genera were strongly connected to very low-density Lp particles of different diameters: Extra small, small, medium, large, very large and extra-large. Another research that was conducted lately demonstrated that in healthy patients' low diversity of intestinal microbiota was connected to adiposity, abdominal adiposity and decreased HDL-cholesterol values. This evidence supports the idea that imbalanced intestinal microbiota might contribute to the changes in very low-density Lp particle size. Thereby, the intestines may be the main source of modified very low-density Lp, though the nutrition might actually be the root cause. Consumption of foods high in carbohydrates leads to an increase in large VLDL particles rich in triglycerides and enrichment of apolipoprotein C proteins, it also elevates the rate of very-low-density Lp triglyceride secretion by the liver but does not alter the apolipoprotein B secretion. This process results in the formation of large and dense very-low-density Lp (Choi and Ginsberg, 2011).

Discussion

This review delves into the intricate role of Very-Low-Density Lipoprotein (VLDL) in atherosclerosis and

cardiovascular diseases, shedding light on various aspects of VLDL composition, classification, metabolism and physiological functions. It presents novel insights that enrich our understanding of how VLDL impacts the development of atherosclerotic lesions, liver disorders, obesity, insulin resistance, coronary artery disease and other related conditions.

One area of focus is the classification of VLDL based on particle charge, a perspective introduced by Avogaro and colleagues, offering a unique approach to discerning the diversity of VLDL particles beyond traditional size-based categorization. This discussion underscores the potential influence of particle charge on VLDL functions and interactions within the body.

Moreover, the review highlights the connection between gut microbiome composition and alterations in VLDL particle size. Specific microbial families are associated with different VLDL subclasses, indicating a potential link between gut health, lipid metabolism and VLDL characteristics. This insight hints at the importance of exploring the interplay between gut microbiota and VLDL dynamics in health and disease.

Additionally, the review discusses genetic variants linked to VLDL particles, such as variants associated with HIF3A and ANKRD55 loci, emphasizing the genetic regulation of VLDL size and composition. Understanding the genetic factors influencing VLDL properties can offer valuable insights into individual susceptibility to cardiovascular diseases and metabolic disorders.

By elucidating the intricate relationship between VLDL, LDL and HDL in promoting atherogenic changes, the review provides a comprehensive view of how VLDL influences lipid exchange reactions and atherosclerosis development. This exploration of the interactions between VLDL and other lipoproteins reveals the complex interplay of these particles in cardiovascular pathophysiology.

Lastly, the review underscores the therapeutic potential of targeting VLDL to prevent atherosclerosis and improve cardiovascular health. The insights derived from this review pave the way for developing novel therapeutic strategies aimed at modulating VLDL metabolism and functions to mitigate the impact of VLDL-related disorders on human health. Overall, these novel insights contribute to a deeper understanding of VLDL's mechanistic implications and provide a foundation for further research and clinical interventions in the field.

Conclusion

In conclusion, the multifaceted discussion in this review underscores the pivotal role of Very-Low-Density Lipoprotein (VLDL) in shaping atherosclerosis, cardiovascular diseases and metabolic disorders. From exploring VLDL composition and metabolism to unraveling its interactions with genetic factors and gut microbiota, this review offers a comprehensive perspective on the intricate mechanisms underlying VLDL-mediated pathophysiology. The identification of potential therapeutic targets within the VLDL pathway opens new avenues for the development of targeted interventions aimed at ameliorating VLDL-related conditions and improving cardiovascular outcomes. Through continued research and clinical translation of these findings, we can advance our understanding of VLDL biology and work towards more effective strategies for managing VLDL-associated health challenges.

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Author's Contributions

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Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

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