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Review

High-density lipoproteins (HDL): Novel function and therapeutic applications

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ABSTRACT

The failure of high-density lipoprotein (HDL)-raising agents to reduce cardiovascular disease (CVD) together with recent findings of increased cardiovascular mortality in subjects with extremely high HDL-cholesterol levels provide new opportunities to revisit our view of HDL. The concept of HDL function developed to explain these contradictory findings has recently been expanded by a role played by HDL in the lipolysis of triglyceride-rich lipoproteins (TGRLs) by lipoprotein lipase. According to the reverse remnant-cholesterol transport (RRT) hypothesis, HDL critically contributes to TGRL lipolysis via acquirement of surface lipids, including free cholesterol, released from TGRL. Ensuing cholesterol transport to the liver with excretion into the bile may reduce cholesterol influx in the arterial wall by accelerating removal from circulation of atherogenic, cholesterol-rich TGRL remnants. Such novel function of HDL opens wide therapeutic applications to reduce CVD in statin-treated patients, which primarily involve activation of cholesterol flux upon lipolysis.

1. Introduction to HDL

High-density lipoprotein (HDL) is a complex family of lipoprotein particles constituted of diverse biomolecules, which primarily include proteins and lipids. Glycosylation of protein and lipid moieties as well as different microRNAs transported by HDL add another dimension to the complexity of this lipoprotein class. Particle content of individual HDL components is not uniform during HDL lifecycle. Instead, continuous recruiting, assembly and breakdown of components play an important role in the dynamic state of HDL particles [1].

1.1. Composition

1.1.1. Proteins

HDL displays the highest density of 1.063–1.21 g/ml among plasma lipoprotein classes, consistent with its elevated protein content comprising approximately a half of total HDL mass [2]. As a corollary, advanced proteomic analysis reveals striking diversity of HDL-associated proteins which can be classified in several subgroups, including apolipoproteins, enzymes, cell-defence proteins, acute-phase proteins and platelet-related proteins, among others.

1.1.1.1. Apolipoproteins. Apolipoprotein A-I (ApoA-I) is a major component of HDL defining both structure and function of this lipoprotein. It is the most abundant protein of HDL accounting for approximately 70% of total protein mass. ApoA-I is mainly secreted by the liver and the intestine [2,3]. Detergent-like properties of ApoA-I enable efficient lipid binding and structural organisation of lipid complexes in nascent HDL. Additionally, by activating lecithin-cholesterol acyltransferase (LCAT), apoA-I plays a critical role in creating spherical HDL particles [2].

Apolipoprotein A-II (ApoA-II), at 15–20 wt% of total HDL protein, is quantitatively the second most abundant apolipoprotein in HDL followed by other apolipoproteins, including apoC-I, apoC-II, apoC-III, apoE, apoM, apoA-IV, apoA-V and apoJ [2]. Although present in minor amounts, these biomolecules play an important role in HDL metabolism, ensuring homeostatic regulation of the overall lipid flux. For example, apoC-II functions as an activator of several triacylglycerol lipases, including lipoprotein lipase (LPL) [4], while apoC-III inhibits LPL and hepatic lipase (HL), decreasing the release of fatty acids form chylomicrons and their uptake by hepatic cells [2]. ApoE serves as a ligand for apoB/apoE receptors, ensuring the internalization of large, light HDL via interaction with the LDL receptor, and possesses antioxidative

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properties. The presence of apoE increases the rate of cholesterol accumulation in HDL [5].

1.1.1.2. Enzymes. Enzymes carried by HDL catalyse reactions that affect multiple aspects of HDL structure and function. LCAT continuously esterifies free cholesterol (FC) within HDL particles, forming spherical HDL; this reaction contributes to cellular cholesterol efflux to HDL [2]. HDL-associated paraoxonase 1 (PON1) and platelet-activating factor acetylhydrolase (PAF-AH) degrade lipid oxidation products, inhibiting low-density lipoprotein (LDL) oxidation and diminishing oxidative damage to the endothelium. These mechanisms underlie anti-inflammatory effects of both PON1 and PAF-AH, since oxidized phospholipids, cellular cholesterol accumulation and thrombosis all induce a proinflammatory response.

1.1.1.3. Lipid transfer proteins. Lipid transfer proteins regulate complex pathways involved in HDL metabolism, ensuring interactions between HDL and other lipoprotein particles, primarily triglyceride-rich lipoproteins (TGRLs). Cholesteryl ester transfer protein (CETP) facilitates bidirectional movement of cholesteryl ester (CE) and triglyceride (TG) molecules between HDL and apoB-containing lipoproteins [6]. By enriching HDL particles with TG and TGRL particle with CE, CETP ensures both rapid catabolism of HDL and transport of cholesterol to the liver for excretion via the LDL receptors (LDL-R). Phospholipid transfer protein (PLTP) exchanges phospholipids between HDL particles as well as across plasma lipoproteins [7]. In addition to providing surface components, PLTP supplies phospholipid substrates for CE production by LCAT, which in turn contributes to HDL maturation.

1.1.2. Lipids

HDL features rich lipidome characterised by the presence of over 200 individual molecular lipids species identified thus far [8]. Lipids are present in HDL particles at a wide concentration range and predominantly include phospholipids, sphingolipids, neutral lipids and steroids.

1.1.2.1. Phospholipids. Phospholipids are polar lipids that dominate the HDL lipid spectrum, accounting for 40 to 50 mol% of total lipid. They are followed by cholesteryl esters (30 to 40 mol%), TG (3 to 5 mol%), and FC (5 to 10 mol%). Phosphatidylcholine (PC, 32–35 mol% of total lipid) is the major structural phospholipid of HDL [8]. PC species in HDL are subjected to regulated lipolytic degradation which produces lysophosphatidylcholines (1.4–8.1 mol% of total HDL lipids) [3]. Phosphatidylethanolamine and plasmalogens comprise approximately 1 mol% of total lipid in HDL and may play a role under conditions of metabolic stress, such as inflammation and oxidative damage [8]. Lipidomic analyses equally reveal the presence of several negatively charged minor phospholipids (0.8 mol% of total lipid), including phosphatidylinositol, phosphatidylserine, phosphatidylglycerol, phosphatidic acid and cardiolipin, which are asymmetrically distributed across HDL subpopulations [9]. The negative charge of these lipids can be important for lipoprotein interactions with enzymes, extracellular matrix and cell surface receptors [9].

1.1.2.2. Sphingolipids. Sphingomyelin, the second most abundant HDL surface lipid (5.6–6.6 mol% of total lipid), strongly impacts surface fluidity of HDL, tightening lipid packing in the surface monolayer. Ceramide and sphingosine-1-phosphate (S1P) constitute two bioactive sphingolipids in HDL present in minor amounts (< 0.1 mol% of total lipids).

1.1.2.3. Steroids. Cholesterol is the main steroid present in HDL. FC is gradually loaded in HDL and controls its surface fluidity. Most of the incorporated FC is thought to be transformed to CE by LCAT, moving to the non-polar HDL core and regulating the capacity of HDL to acquire FC from peripheral tissues. The core also contains small amounts of triacylglycerides whose main species carry oleic, palmitic and linoleic acid moieties [3]. Finally, HDL possesses minor amounts of diacylglycerides, monoacylglycerides and free fatty acids [3].

1.1.3. Carbohydrates

Several HDL proteins (up to 3.3 wt% of total protein) undergo enzymatic glycosylation, widening their structural and functional heterogeneity. Products of both N- (predominantly) and O-linked glycosylation can be found in HDL [10]. Our recent N-glycome profiling of HDL reveals more than 20 individual glycomic moieties, manifesting the presence of complex combinations of galactose, high-mannose and hybrid N-glycans which are frequently (by ~70%) attached to one or two sialic acid residues at their biantennary termini [10].

1.1.4. MicroRNAs

HDL transports several microRNAs (miRs), which may constitute an alternative form of intercellular signalling mediated by HDL. HDL-associated miRs can reach their target cells either by direct delivery into the cytoplasm via whole HDL particle uptake or through scavenger receptor BI (SR-BI) [11]. Despite the presence of low copy numbers of miRs in HDLs, some evidence suggests that HDL-associated miRs are functionally relevant. For example, delivery of miR-223 by HDL into endothelial cells can suppress intercellular adhesion molecule 1 (ICAM-1) expression [12].

1.2. Heterogeneity

HDL represents a highly heterogeneous class of lipoproteins both physically and chemically [2]. As a consequence, HDL subpopulations widely differ in their function [9]. Conformational flexibility of apoA-I and continuous intravascular remodelling drive phenotypic variability of HDL particles [13]. Indeed, although newly generated HDL are discoid in shape, small-sized and poorly lipidated, gradual movement of cholesterol to the non-polar particle core following esterification by LCAT creates a spectrum of spherical HDL particles of larger size and lower density. Agarose gel electrophoresis enables separation of preβ-migrating particles, consisting of nascent discoid and poorly-lipidated HDL, and mature, lipid-rich α-migrating particles which predominate in the circulating HDL pool [13]. Furthermore, combination of agarose and gradient gel electrophoresis enables identification of up to 12 distinct apoA-I-containing HDL subclasses, including preβ1, preβ2, α1, α2, α3, α4, preα1, preα2 and preα3 particles.

Next, HDL subpopulation of different size (large, medium and small) can be quantified using NMR [13]. In addition, sequential ultracentrifugation allows isolating two major HDL subclasses, including light, lipid-rich HDL2 (d 1.063–1.125 g/ml) and dense, protein-rich HDL3 (d 1.125–1.21 g/mL), which can be further fractionated into large HDL2b and 2a and small HDL3a, 3b and 3c by isopycnic density gradient ultracentrifugation [13].

1.3. Epidemiology

Low plasma concentrations of HDL-cholesterol (HDL-C) are firmly established as a cardiovascular (CV) risk factor [2]. This finding underlies our ongoing interest to HDL. Recent large-scale epidemiological studies however unambiguously document paradoxically increased CV and overall mortality at extremely high HDL-C levels. Such observations were made in the CANHEART cohort in Canada [14], two prospective population-based studies in Denmark [15], nine Japanese cohorts [16] and in several other populations. These reports consistently reveal U-shaped relationships of HDL-C with both CV and non-CV mortality following multifactorial adjustment. Similar U-shape relationships of HDL-C with mortality were equally observed for other disorders, including infectious and autoimmune diseases [17,18]. These

data suggest that there is a range of optimal HDL-C levels outside of which HDL-C may be associated with elevated disease risk. The common belief that the higher HDL-C the better does not therefore hold for extremely high concentrations [15]. Prevalence of such extreme HDL-C concentrations is however rare in a general population as their reported frequency varies from 2.0 to 2.9% [15,19,20].

The descending part of the U-shape relationship can be accounted for by the observation that subjects with low HDL-C typically display elevated burden of comorbid illnesses, including cardiovascular disease (CVD), cancer and Type 2 diabetes [14]. Low HDL-C may thus represent a non-specific marker of poor general health [14]. There is however no obvious explanation for the increased mortality observed in subjects with extremely high HDL-C levels. Indeed, while such individuals are predominantly women and present with excess alcohol consumption, they may feature improved socioeconomic characteristics and healthy lifestyle [14,16].

In patients treated with statins, the relationship between low HDL-C and CVD is typically weakened [14] and can disappear [21,22]. Interestingly, the association of extremely high HDL-C with CVD was absent in statin users [14]. HDL-C concentration is therefore probably not useful as a biomarker in secondary prevention.

1.4. Genetics

The U-shape relationship between HDL-C and mortality can potentially be explained by an association of both low and extremely high HDL-C concentrations with genetic variants associated with CVD. However, genetically altered HDL-C concentrations do not necessarily lead to elevated CV risk.

1.4.1. Low HDL-C

Mutations in the *APOA1*, ATP-binding cassette transporter A1 (*ABCA1*) or *LCAT* genes resulting in low HDL-C are not always associated with accelerated CVD. For example, while homozygous apoA-I deficiency results in premature atherosclerosis, some heterozygous apoA-I mutations, such as apoA-I Milano and Paris, paradoxically decrease CV risk [23].

Next, extremely low HDL-C levels observed in inherited disorders of HDL metabolism involving rare mutations of ABCA1 or LCAT are inconsistently associated with CVD and atherosclerosis [23,24]. Indeed, atherosclerosis is accelerated in heterozygous LCAT deficiency also known as fish-eye disease, while homozygous familial LCAT deficiency results in reduced atherosclerosis [25]. Tangier disease, a rare monogenic autosomal recessive disorder, is derived from ABCA1 mutations which lead to markedly reduced HDL-C levels and frequently result in elevated CV risk which can however be markedly modified by reduced LDL-cholesterol (LDL-C) concentrations [26].

1.4.2. Extremely high HDL-C

Certain mutations in *CETP*, hepatic lipase (*LIPC*) and SR-BI (*SCARB1*) are associated with both extremely high concentrations of HDL-C and elevated risk of coronary heart disease, and may thereby exert detrimental effects on mortality [15]. Indeed, a rare loss-of-function P376L variant in *SCARB1* raises HDL-C and increases risk of coronary heart disease (CHD) [27]. However, carriers of a missense P297S mutation display increased HDL-C but carotid artery intima-media thickness (IMT) is similar in carriers and family controls [28]. Highly elevated HDL-C due to genetically compromised SR-BI function is therefore not always a marker of increased coronary artery disease (CAD) risk [29].

In a similar fashion, patients with CETP deficiency feature markedly increased HDL-C levels which are sometimes accompanied by accelerated CVD [30]. Elevated HDL-C concentrations resulting from alterations in the *CETP* gene are however more consistently associated with reduced CV risk [31], potentially reflecting concomitant decreases in TG, LDL-C, and non-HDL-C levels [31]. Consistent with this conclusion, Mendelian randomization does not reveal causal relationships between HDL-C and CV risk in carriers of the *LIPG* rs61755018 variant [32]. In this study however, control subjects displayed HDL-C levels of 50 mg/dl or higher, which were modestly (by +3 to +11 mg/dl) increased in the carriers. According to the U-shape epidemiology [14–16], modest HDL-C increases in this range do not necessarily result in cardioprotection. It should be also kept in mind that variants in HDL-associated genes jointly account for very little of the variance in HDL-C levels and may exert pleiotropic effects [33]. In addition, Mendelian randomization studies are based entirely on SNPs and typically exclude most important genes that regulate HDL-C levels, notably *ABCA1, LCAT, APOA1*, and *LPL*. Such manual pruning of SNPs might result in a genetic instrument that is no longer biologically meaningful [34].

1.5. Function

1.5.1. The HDL hypothesis and RCT

To explain the association between low HDL-C and CVD, HDL was proposed to exert a biological function resulting in atheroprotection, which is compromised when HDL-C is low. Negative correlations between body cholesterol pools and HDL-C as well as negative correlations of HDL-C with LDL-C and very low-density lipoprotein (VLDL)-TG allowed Miller and Miller to postulate that HDL clears cholesterol from the arterial wall [35]. As a corollary, atherosclerosis was proposed to reflect delayed cholesterol clearance from the arteries secondary to reduced HDL levels in plasma. Such HDL hypothesis was based on the concept of reverse cholesterol transport (RCT) from peripheral tissues to the liver earlier developed by Glomset [36].

Subsequent studies identified major elements of the RCT pathway which are presently thought to include efflux of cellular cholesterol from ABCA1-expressing peripheral cells to lipid-free/lipid-poor apoA-I, formation of nascent HDL, esterification of FC in nascent HDL by LCAT, transfer of esterified cholesterol from HDL to the liver and excretion of HDL-derived cholesterol to the bile in a form of bile salts. According to the RCT hypothesis, cholesterol efflux from arterial wall cells with its subsequent transport to the liver represents the major atheroprotective function of HDL [37]. As a consequence, delayed cholesterol efflux from the arterial wall impairs RCT and accelerates atherosclerosis. This hypothesis is supported by negative associations of CVD with in vitro measurements of cellular cholesterol efflux from lipid-loaded macrophages [38].

1.5.2. Other HDL functions

Decades of further research has extended our understanding of HDL from a sole lipid-carrying particle ensuring cholesterol clearance to multiple other aspects, including antioxidative, antiinflammatory, vasodilatory, antiapoptotic, antithrombotic and antiinfectious activities [39]. Such functions are frequently deficient in metabolic diseases involving accelerated CVD and low HDL-C levels but their relationships to CV morbidity and mortality remain indeterminate.

Overall, mechanisms underlying functional activities of HDL can be associated to HDL capacity (i) to efflux cholesterol from cells, (ii) to activate downstream signalling pathways via ligand-stimulated receptors or cholesterol availability in lipid rafts, and (iii) to inactivate bacterial toxins and oxidized lipids by specific lytic factors and through hydrolysis, respectively [2,40]. Furthermore, individual properties of HDL may act cooperatively to ensure functional effects of the lipoprotein [2].

Complex composition and high heterogeneity of HDL constitute the principal foundation for explaining its diverse functionality [39,41]. Interestingly then, individual HDL subspecies differ in their biological functions. Indeed, small, dense, protein-rich HDLs typically display potent anti-atherogenic activities, reflecting their distinct content of multiple protein and lipid components [9].

1.5.3. The HDL function hypothesis

Negative results of Mendelian randomization studies which did not find causal relationships between HDL-C and CVD [32,42] led to the revision of the HDL hypothesis to include the statement that accelerated atherogenesis results from a deficiency in a cardioprotective HDL function rather than from reduced HDL-C levels per se [37]. Such HDL function hypothesis implies that such cardioprotective function of HDL (which most often is thought to include cholesterol removal from arterial macrophages) cannot always be reliably estimated through the assay of HDL-C. Although proposing a plausible explanation for the absence of causal relationships between HDL-C and CVD, the hypothesis has several limitations. First, removal of cholesterol from human atherosclerotic intima through RCT was not directly demonstrated in humans [43]. Second, the capacity of HDL to penetrate the endothelium, remove cellular cholesterol from macrophages and exit to the plasma compartment carrying such cholesterol remains to be firmly established [44]. Third, measurements of RCT using labelled cholesterol reveal absence of correlation between tissue cholesterol efflux and HDL-C in humans [45]. Consistent with these data, cholesterol efflux from tissue macrophages provides only a minimal contribution to HDL-C levels [46]. Indeed, as macrophages comprise only a small portion of total peripheral cells, only a minor part of HDL-C can originate from the macrophages.

Most importantly, the HDL function hypotheses can hardly explain the U-shape association between HDL-C and CVD. In order to account for this relationship, cardioprotective function of HDL should be compromised at both low and extremely high HDL-C levels. HDL function is indeed frequently deficient in subjects with low HDL-C [39]. By contrast, cholesterol removal from peripheral cells is unlikely to be deficient in subjects with extremely high HDL-C. Indeed, cholesterol efflux capacity of HDL from human macrophages is enhanced in subjects with high HDL-C levels who carry variants in the CETP or LIPC gene [47] and in CETP-deficient subjects displaying extremely high HDL-C [48]. On the other hand, anti-inflammatory activity of HDL was reportedly reduced in CHD patients with extremely high HDL-C [49]. In addition, angiogenic properties of HDL evaluated in vitro as tube formation in endothelial progenitor cells are weakened at high concentrations of the lipoprotein [50]. Relevance of this pathway for human atherogenesis however remains unclear.

1.6. Metabolism

1.6.1. Production

HDL is classically thought to be produced in several steps with a participation of membrane-bound and plasma proteins. HDL production is centred on apoA-I, the major HDL component, which is mainly produced and secreted by the liver and the intestine in comparable amounts [51]. ApoA-I is secreted by hepatocytes in either lipid-free or lipid-poor form. Initial HDL assembly typically involves transfer of membrane phospholipids and cholesterol to lipid-free/lipid-poor apoA-I, which occurs at the cell surface and represents the first step of the RCT pathway. ABCA1, a ubiquitous trans-membrane protein which functions as a membrane phospholipid translocase, ensures such transfer across a cell plasma membrane to apoA-I bound to the cell surface. This activity results in the formation of discoid nascent HDL particles, increasing the stability of apoA-I in the circulation and preventing its rapid elimination through the kidney. Other apolipoproteins, including apoA-II, apoA-V, apoC-I, apoC-II, apoE and apoM, are also capable of forming nascent HDL upon interaction with ABCA1.

In the next step, FC is transferred from the surface monolayer to the hydrophobic core of HDL following its esterification by LCAT, creating mature spherical HDL. This reaction further delays catabolism of apoA-I, resulting in the accumulation of spherical HDL particles which predominate in the plasma HDL pool. Conversion of FC into CE by LCAT maintains a gradient of FC between the lipoprotein surface and the peripheral cell membrane, ensuring FC removal from cells [52]. Reflecting preferential association of LCAT with HDL, approximately 70% of total plasma CE production occurs in this lipoprotein, with the rest occurring in apoB-containing particles [53].

1.6.2. Remodelling and catabolism

HDL is remodelled and catabolised upon interactions with cellular receptors, lipid transfer proteins and enzymes.

Mature spherical HDL can further increase in size through effluxing cellular cholesterol and phospholipid via ABCG1 [54] and SR-BI [55]. CETP accelerates catabolism of HDL particles via their enrichment in TG, while PLTP converts HDL into both larger and smaller subspecies [7].

Lipases modify both surface and core lipids of HDL. Thus, endothelial lipase (EL) primarily hydrolyses HDL phospholipids but also breaks down TGs. By contrast, HL hydrolyses primarily tri- and diglycerides but also breaks down HDL phospholipids. As a result, both lipases efficiently reduce HDL particle size.

Hepatic removal of cholesterol from HDL occurs at the surface of hepatocytes when CE molecules are selectively taken up from large, spherical, cholesterol-rich HDL to the cells via SR-BI. Small, dense HDL particles depleted of CE are regenerated in this process which constitutes the last step of the RCT pathway.

Following hepatic removal, HDL-derived cholesterol is secreted into the bile [56]. Direct excretion of cholesterol can also occur in the proximal small intestine. While HDL proteins are catabolysed in the liver and the kidney, HDL particles can be removed from plasma by holoparticle HDL receptors, including cubulin and ectopic β-chain of ATP synthase [2].

1.7. Therapeutic applications

With low plasma HDL-C established as a strong and independent CV risk factor, the concept of therapeutic HDL-C-raising started to being developed as a novel approach to reduce CVD [2]. This concept however resulted in multiple failures involving CETP inhibitors, reconstituted HDL (rHDL) infusions, and other approaches [22]. Together with the data obtained in Mendelian randomization studies [32], such negative results of clinical trials casted doubt on the therapeutic value of HDL-C-raising.

1.7.1. CETP inhibitors

CETP inhibitors potently increase HDL-C and decrease LDL-C, TG and apoB, albeit to a lesser extent. Torcetrapib was the first CETP inhibitor that entered large-scale trials which unexpectedly revealed elevated mortality upon treatment in patients receiving statins [57]. This failure was followed by the futility of the trials of dalcetrapib [58] and evacetrapib [59] equally performed on a statin background. Only anacetrapib provided a modest clinical benefit in a similar setting [60] but the effect was less than expected. Although the excessive mortality caused by torcetrapib was ascribed to off-target hypertensive effects [61], development of CETP inhibitors was largely deemed unsuccessful.

CETP inhibitors raise HDL-C by depleting HDL of TGs and thereby delaying HDL catabolism [62]. If the flux of cholesterol from the periphery to the liver through the RCT pathway is central for the link between low HDL-C and atherosclerosis, then delayed catabolism of HDL should not necessarily lead to accelerated removal of cholesterol from the arterial wall. Indeed, CETP inhibitors do not enhance RCT in vivo to excrete cholesterol into feces [30,63]. Furthermore, the concept of CETP inhibition is not directly supported by the kinetics of cholesterol metabolism in humans. Indeed, circulating CE is predominantly removed from the circulation via apoB-containing lipoproteins rather than from HDL [53,64].

1.7.2. Fibrates

Fibrates are PPAR-alpha agonists which raise HDL-C and decrease TG, primarily acting via activation of LPL and enhancement of apoA-I production. Although fibrates are presently not recommended in combination with statins for CVD prevention, patients with high TG levels and low HDL-C might still benefit from fibrate therapy [65]. Beneficial effects of fibrates can be mediated, among other pathways, through the elevation in the concentration of small HDL particles possessing potent atheroprotective activities [66].

1.7.3. Niacin

Similar to fibrates, niacin raises HDL-C and decreases TG, primarily acting via inhibition of hormone-sensitive lipase and diacylglycerol acyl transferase 2 (DGAT2). Although being inefficient in combination with statins [67], extended-release niacin can significantly reduce CVD in a subgroup of patients with high TG and low HDL-C [68].

1.7.4. HDL infusions

Originally considered therapeutically promising [69], infusions of reconstituted HDL (rHDL) finally failed to provide clinical benefit in statin-treated patients. For example, CER-001 did not reduce coronary atherosclerosis and CV events in patients with acute coronary symptoms [70,71]. Importantly, earlier studies reporting beneficial effects of rHDL infusions on coronary atherosclerosis were largely performed in patients who were not on statins [69].

1.7.5. Potential reasons for the failure of HDL-C raising

The negative results of the HDL-C-raising trials can potentially be accounted for by the elevated CV and overall mortality at extremely high HDL-C levels observed in epidemiological studies [14–16]. Indeed, several HDL-C-raising agents, primarily CETP inhibitors, resulted in extremely high on-treatment levels of HDL-C [72].

Another reason for the absence of clinical benefit of HDL-C-raising may theoretically involve lack of beneficial effects on atheroprotective HDL functions [73]. This possibility is however inconsistent with the observation of enhanced cholesterol efflux capacity of HDL from mouse and human macrophages after treatment with CETP inhibitors or niacin [33,74,75].

More probably, potential benefits of HDL-C-raising were offset by statin treatment. Indeed, all modern large-scale clinical trials of HDL-C-raising agents were performed on a background of statins which presently represent a standard of care. In contrast to earlier trials carried out in the pre-statin era, HDL-C-raising agents did not exert beneficial effects on CVD in patients receiving statins [76]. Consistent with these data, systematic review of the effects of HDL-C-raising drugs reveals that they are efficient at high baseline LDL-C [77]. Mechanisms through which CETP inhibitors, fibrates and niacin increase HDL-C are distinctly different, suggesting that potential benefits of HDL-C-raising are offset by statins independently of the mechanism of HDL-C-raising.

2. Novel insights into HDL

2.1. Metabolism

The widely accepted view of HDL evolving from small nascent particles to large spherical lipoproteins whose function is to deliver cellular FC to the liver in the form of CE following esterification by LCAT has recently been challenged by several studies.

Indeed, endogenous isotopic labelling reveals that progressive enlargement of very small and medium to large and very large HDL as well as generation of very small from medium HDL are minor metabolic pathways in humans [78]. Unexpectedly, HDL appears to be secreted into the circulation in its entire size distribution from very small to very large particles. The processes of cholesterol uptake and transfer into and out of HDL occur mainly within rather than between HDL subpopulations which do not experience major changes in size. For example, when hepatic SR-BI selectively takes up CE from HDL, the efflux of CE from each HDL particle is balanced by the influx of cholesterol from cells [78]. Cholesterol uptake from cells mediated by HDL can also be compensated by CETP-mediated CE transfer from HDL to apoB-containing lipoproteins. Stability of HDL size can be equally maintained under the action of HL which hydrolyses excessive TG delivered to HDL by CETP. Uptake and esterification of cellular cholesterol by small discoidal HDL which subsequently grow in size thereby represent a minor pathway [78].

Consistent with this conclusion, isotopic studies performed in humans and mice show that FC esterification by LCAT is a minor process in HDL metabolism [79,80]. Furthermore, studies in humans demonstrate that little CE is transported directly from HDL to the liver [64]. As a result, selective CE uptake from HDL does not appear to represent the major route of CE elimination from the circulation in humans. Instead, CE is predominantly delivered to the liver from apoB-containing lipoproteins [53].

In contrast to CE, FC is rapidly transferred from both nascent and mature HDL to the liver independent of LCAT activity and secreted in the bile or utilized as the primary precursor for bile acid synthesis [80]. There is marked output of FC from HDL of approximately 30% of total cholesterol output from the circulation. Furthermore, multicompartmental modelling reveals extensive exchange of FC between HDL, blood cells and other tissues [80]. HDL therefore plays a central role in FC exchange and transport between all tissues and plasma [64]. This conclusion is further supported by a discordance between relatively high tissue cholesterol efflux of 4 mg/kg/day and low plasma CE production of approximately 1 mg/kg/day measured using constant ^{18}C infusion in human subjects [45]. This result suggests that the majority of tissue cholesterol efflux occurs via FC which is rapidly redistributed among plasma lipoproteins [45]. Indeed, FC flux through plasma is an order of magnitude faster than that of CE [81]. FC clearance kinetics in humans is rapid; indeed, most plasma HDL-FC is cleared with $t_{1/2}$ about 8 min, during which only 5% of FC is converted to CE [80].

Consistent with these data, isotopic studies in mice show that most FC is rapidly extracted from nascent HDL by the liver via SR-BI and by spontaneous transfer [79]. As a corollary, FC is accumulated in HDL in the absence of functional SR-BI as revealed by experiments in SR-BI$^{-/-}$ mice [80]. In a cellular model, FC and PL are rapidly transferred from HDL to the plasma membrane of SR-BI-expressing Chinese hamster ovary cells when CE is still associated with the particles [82].

Together, these data strongly suggest that HDL-mediated RCT predominantly involves transport of FC, which occurs mainly within rather than among HDL subpopulations. Much cholesterol in the RCT pathway enters and exits medium and large size HDL without changing a size category [83]. In this model, all sizes of HDL are secreted into plasma, circulate mainly within their secreted size and take up FC from cells [78,83]. ApoA-I–containing HDL is thereby secreted into the circulation as mostly spherical CE–rich lipoproteins that span the HDL size range, whereas discoidal, cholesterol-poor HDL comprises a minority of HDL secretion. Importantly, clearance of FC from plasma does not appear to require the esterification step that is implicated in the conventional RCT model [80]. The focus of cholesterol clearance, and RCT, should therefore shift to FC rather than the current focus on HDL–C and HDL–CE.

2.2. Links to TGRL

TGs serve as a major energy source in mammals. Intravascular lipolysis of TGRLs, both chylomicrons and VLDL, by LPL is an essential element of energy production aimed at the release from TGs of free fatty acids which are used as a source of energy in a process of beta-oxidation. TGRL metabolism is intimately linked to that of HDL, a phenomenon which is reflected by a negative correlation between plasma

levels of TGs and HDL-C [84,85]. This correlation results from complex interactions between HDL and TGRL mediated by multiple metabolic pathways. Thus, CETP-mediated heteroexchange of CE and TG between mature spherical HDL and apoB-containing lipoproteins, primarily TGRLs, leads to the formation of TG-enriched HDL which are readily lipolysed by HL, decreasing HDL size and accelerating HDL clearance from the circulation [6]. The role of CETP in HDL metabolism is well-known and remains beyond the scope of the present review.

Moreover, TGRL and HDL are metabolically linked via transfer from TGRL to HDL of surface remnants generated during TGRL lipolysis by LPL [86]. This well-known, but frequently overlooked, pathway delivers high amounts of FC and phospholipid to HDL and represents a major source of circulating HDL–C, accounting for up to 50% of its variation [87].

2.2.1. Introduction to TGRL

Circulating TGRL is atherogenic as evidenced by both epidemiological and clinical studies. TGRL levels are genetically regulated and can be therapeutically normalised using several approaches.

2.2.1.1. Epidemiology. Epidemiological studies reveal that elevated concentrations of TGs are causally related to CVD and all-cause mortality [84]. Elevated plasma TG levels represent biomarkers of the accumulation of atherogenic, cholesterol-rich TGRL particles which include chylomicron remnants, VLDL, and intermediate-density lipoproteins (IDL) [84]. The TGRL remnants carry large proportion of total plasma cholesterol of approximately one third [88]. Consistent with this observation, remnant cholesterol defined as the cholesterol content of all TGRLs was shown to be more atherogenic than LDL-C [84,89]. Indeed, a TGRL particle can carry 5 to 50 times more cholesterol per particle than LDL [85].

As plasma levels of remnant cholesterol parallel those of TG and the latter are inversely correlated with HDL-C, remnant cholesterol is equally correlated negatively with HDL-C [84]. Low HDL-C can therefore be regarded as a stable marker of elevated concentrations of TGs and remnant cholesterol, which is statistically more strongly associated with CVD than TGs [90]. As a consequence, low HDL-C is typically observed in combination with elevated TG, while isolated low HDL-C is uncommon (2.3% as reported by the Framingham Offspring Study) [91].

2.2.1.2. Genetics. Specific genetic mechanisms that increase plasma TGRL and augment CV risk include loss of LPL function, loss of apoA-V function, gain of angiopoietin-like protein (ANGPTL) 4 function and gain of apoC-III function [85]. Plasma HDL-C is typically reduced under these conditions. By contrast, gain of LPL function and loss of apoC-III and ANGPTL4 functions can be cardioprotective. Mechanistically, the association between apoC-III and CVD primarily reflects inhibition of LPL-mediated TG lipolysis and of hepatic TGRL uptake [85]. In addition, apoC-III impairs antiatherogenic properties of HDL. In a similar fashion, LPL activity can be inhibited by ANGPTL3 and ANGPTL4 [92].

2.2.1.3. Atherogenicity. Intact native TGRLs are not directly atherogenic as they are too large to enter into the arterial intima [84]. In contrast to native TGRLs, some of their remnants can be small enough to cross the endothelium and can therefore be atherogenic. Altered metabolism of TGRL particles results in the accumulation of their remnants in the circulation and the arterial wall. Indeed, atherosclerotic lesions in both humans and experimental animals contain numerous, large, extracellular, liposome-like particles, which differ from extracellular VLDL- and LDL-like particles and intracellular lipid droplets [93]. Such TGRL remnants can be taken up in an unregulated fashion by scavenger receptors of arterial wall macrophages which thence become foam cells [93]. In addition, TGRL remnants are cytotoxic and pro-inflammatory [94].

2.2.1.4. Therapeutic normalisation. Plasma TG levels constitute promising therapeutic target in patients treated by statins. TG lowering is typically achieved through therapeutic modulation of the LPL pathway, either by direct enhancement of LPL activity or by blocking of the effects of natural LPL inhibitors, such as apoC-III and ANGPTL4 [85].

As a result, TG lowering bears a potential to reduce residual CV risk remaining in patients treated by statins. Indeed, 2 g of icosapent ethyl twice daily significantly decreased risk of ischemic events, including CV death, in statin-treated patients with elevated TG levels as compared to those who received placebo [95]. Furthermore, treatment with TG-lowering agents, including fibrates, niacin and omega-3 fatty acids, significantly reduced major CV events, CV mortality and myocardial infarction in a meta-analysis of 30 randomized large-scale clinical trials [96].

2.2.2. TGRL lipolysis

TGRLs are lipolysed in the circulation under the action of LPL, resulting in the formation of remnant TGRL particles. HDL plays a key role in this process, interacting with TGRL via multiple mechanisms.

2.2.2.1. Formation of TGRL remnants. When intestinally-derived chylomicrons or hepatically-derived VLDL enter blood circulation, their TGs are subjected to lipolysis on the endothelial surface. LPL-mediated lipolysis is a rate-limiting step of plasma TGRL catabolism. LPL rapidly converts chylomicrons and VLDL into remnant particles, with a formation of both core and surface TGRL remnants. Indeed, shrinkage of the hydrophobic lipoprotein core leads to the formation of smaller-sized, higher-density remnant TGRLs also called core remnants, including chylomicron remnants, IDL and LDL [97–99]. Intestinal and hepatic TGRL thereby share common removal pathways which are saturable.

Consequently, redundant constituents of the surface monolayer surrounding the hydrophobic core of TGRLs are shed from the particles in a form of surface remnants. Such excess material includes surface apolipoproteins, phospholipids and FC in a form of unstable lipid bilayer sheets and finger-like protrusions which can reorganise into large-size vesicular structures [98,100,101]. Formation of surface TGRL remnants possibly involves spontaneous organisation of excessive surface lipids removed from TGRL into low-energy complexes which resemble micelles or liposomes [93]. In parallel, discoid, lipid-poor, protein-rich particles can be formed from apolipoproteins and surface lipids of the TGRL surface. At the end of their lipolytic catabolism, TGRLs lose more than 90% of their mass during remnant formation [102].

2.2.2.2. Mass exchanges with HDL. In the circulation, surface TGRL remnants predominantly fuse with HDL, adding material to the HDL pool. Potent lipid-acquiring properties underlie efficient lipid transfer to HDL under conditions of TGRL lipolysis. Indeed, HDL can readily acquire exogenous lipids, including both polar (FC, phospholipid) and non-polar (CE, TG) molecules [103]. By contrast, blood cells cannot serve as acceptors of FC released upon TGRL lipolysis [104]. Such preferential transfer of FC to HDL may reflect preferential fusion of surface TGRL remnants with HDL rather than with cell membranes.

TG lipolysis by LPL thereby induces flux of FC from TGRL to HDL, providing substrate for HDL-associated LCAT and increasing HDL-C [105]. In addition, TGRL lipolysis delivers to HDL high amounts of phospholipid, but not of CE [106]. Surface apolipoproteins, including apoC-II, apoC-III and apoE, are equally transferred from TGRL to HDL upon lipolysis in vitro and in vivo [99,101,107–111]. Rapid (within 2 to 60 min) postprandial transfer of surface components from chylomicrons to HDL upon lipolysis can be directly demonstrated using radiolabelled phospholipid, apoA-I and apoA-IV in vivo [108].

As a consequence, HDL-C is positively associated with several metrics of TGRL catabolism. Indeed, both LPL activity and fractional catabolic rate (FCR) of VLDL-derived apoB and TG are positively correlated with plasma HDL-C, apoA-I and apoA-II [86,87]. Variations in the LPL

activity and the rate of TGRL lipolysis may therefore account for a considerable portion of the variability in levels of HDL-C, indicating that HDL-C represents an index of LPL activity [112] and a biomarker of TGRL lipolysis by LPL [113]. Furthermore, TGRL catabolism by LPL can be regarded as a key factor of apoA-I and apoA-II metabolism [86]. Mechanistically, increasing LPL activity accelerates TGRL catabolism, raising HDL-C by enhancing the transfer of surface material from TGRL to HDL and reducing FCR of apoA-I and apoA-II.

The transfer of FC, phospholipid and protein to HDL upon lipolysis is accelerated with increasing VLDL concentration [109]. The presence of HDL enhances TGRL lipolysis, removing lipids and proteins released during this process [101]. During in vitro lipolysis of isolated VLDL, lipolytic surface remnants remain largely attached to the core remnants in the absence of HDL, dissociate to form liposome-like vesicles in the presence of low levels of HDL, and are assimilated into HDL to form larger HDL particles in the presence of high HDL concentrations [93]. Extremely high concentrations of HDL may however delay cholesterol accumulation in HDL upon TGRL lipolysis, acting via FC esterification by LCAT in HDL followed by the transfer to TGRL of CE formed in this reaction [114].

Interestingly, the transfer rate of PL and CE increases with decreasing FC/phospholipid ratio in HDL, suggesting the role of surface area and/or rigidity [111]. In addition, phospholipid transfer from VLDL to HDL upon lipolysis is higher in women vs. men, potentially reflecting elevated lipid surface of acceptor HDL particles in women [111].

2.2.2.3. Formation of large HDL. The size of the acceptor HDL particles is typically increased following TGRL lipolysis, whereas their density is diminished [97,101,109,115]. As a result, large HDL particles are preferentially formed. Indeed, incubation of human serum with LPL results in the accumulation of HDL2 paralleled by the decrease in HDL3 [116]. In addition, lipolysis of VLDL by LPL in the presence of HDL3 reduces phospholipid, FC and total protein in VLDL with their elevation in HDL2. Underlying mechanisms involve transfer of surface constituents from TGRL predominantly to HDL3, which is enlarged to become HDL2a [117], or to both HDL2 and HDL3 [118]. Consistent with these data, small, dense HDL3 particles represent a preferential acceptor for surface lipids and apolipoproteins released from TGRL during lipolysis, potentially reflecting their lipid-poor composition [86,114]. As a result, there is a precursor-product relationship between surface components of TGRL and HDL2 [86]. Negative correlations of the increase in plasma TG with HDL2 mass, TG, phospholipid and protein content observed in healthy subjects following fat load further support this contention [119].

In vivo data confirm preferential formation of large HDL upon TGRL lipolysis by LPL. Thus, HDL size is enlarged, molecular mass elevated and density s diminished after a fat meal [117]. Levels of large, light HDL2 are increased, while those of small, dense HDL3 can be either increased or slightly decreased after such meal [117]. In addition, levels of HDL-C, predominantly those of HDL2-C, are increased following heparin-induced lipolysis [86].

Together, these data reveal that LPL plays a key role in the formation of HDL2 [86]. This conclusion is supported by the observations of elevated LPL activity paralleled by elevated HDL-C levels in females vs. males, in alcohol users vs. non-users, and upon physical activity [86]. Furthermore, HDL capacity to clear TGRL is elevated in women relative to men, a finding which may contribute to the protection from CVD [120]. Postprandial phase may therefore determine elevated HDL concentrations in women.

2.2.2.4. Formation of pre-beta HDL. Small pre-beta HDL particles containing apoA-I and phospholipid can be released from HDL as a result of the transfer of surface material from TGRL during lipolysis [86]. In vitro incubations of VLDL with LPL indeed produce pre-beta-1-HDL whose levels are dose-dependently increased with increasing LPL concentration as well as over time [121]. In addition, small apoA-I-containing HDL is formed upon VLDL lipolysis by LPL in the presence of HDL [115].

Pre-beta-1-HDL is formed in vivo during TGRL lipolysis by LPL induced by heparin injection in healthy men [121]. Mechanisms underlying this process involve acquirement by HDL3 of surface TGRL remnants followed by HDL enlargement to HDL2a and release of pre-beta HDL.

2.2.3. Mechanisms of mass exchanges

2.2.3.1. Role of apoA-I. ApoA-I represents a typical amphipathic protein which binds avidly to lipids [122,123]. Such properties render apoA-I a potent biological detergent which forms stable micellar complexes with phospholipids, FC, TGs and CE. In addition, the protein displays exceptional conformational flexibility, a property which largely underlies high heterogeneity of plasma HDL [3,123]. ApoA-I as well as receptors and transporters involved in HDL and apoA-I metabolism - SR-BI, ABCA1, and ABCG1 - are evolutionarily conserved, suggesting key biological functions [124]. Solubilisation of lipids arguably represents a major biological function of apoA-I, which can be associated with atheroprotection. Indeed, animal experiments consistently reveal that apoA-I protects from atherosclerosis [125]. Other biological activities of apoA-I most relevant in this regard involve its capacity to remove cellular cholesterol and to attenuate inflammation, although they may equally be mechanistically underlain by lipid binding.

ApoA-I is produced by the liver and throughout the small intestine. Frequently neglected, the intestinal production nevertheless provides a major contribution to the plasma pool of apoA-I, which can reach 30–40% of total plasma apoA-I supply in humans [102], although other estimates put it close to 10% [126]. In rats, intestine produces 50 to 56% of total apoA-I and the liver produces the rest [127–129]. In agreement with these data, considerable part (30–40%) of daily body synthesis of apoA-I is carried on intestinal TGRL in man [51]. It is remarkable in this regards that human enterocytes synthesize more apoA-I and apoB than HepG2 cells [130]. Interestingly, apoA-I is specifically concentrated in apoB-48- but not apoB-100-containing TGRL particles [131]. Reflecting strong intestinal production, apoA-I prevails among apolipoproteins of chylomicrons, while apoB is a quantitatively minor component (3.4 wt% of total protein in humans) [102]. In addition, apoA-I is more concentrated (15 to 20%) in human chylomicrons than apoB and becomes a major component in rats (56%) [102,132].

Upon production, apoA-I is secreted by the intestine into the lymph together with other apolipoproteins and lipids primarily as a component of nascent chylomicrons and partly as discoid nascent HDL. ApoA-I synthesis and secretion in the lymph increase with lipid absorption by the intestine [102]. The protein is a major component of mesenteric lymph chylomicrons in rats, accounting for about one-third of total protein mass, with apoB accounting for about 10% [133]. In intestinal lymph, apoA-I accounts for 15–35 wt% of total chylomicron protein with apoB and apoA-IV accounting for 10% each, while the contribution of apoCs prevails at 42–50% [51,98]. As a result, chylomicrons are a major source of plasma apoA-I; indeed, 27% of total body synthesised apoA-I enters plasma on chylomicrons [129].

Following secretion, most of chylomicron apoA-I is transferred to HDL during peripheral lipoprotein catabolism [132]. Similar transfers occur when chylomicrons are incubated in the presence of plasma in vitro [133,134]. While a majority of TGRL-derived apoA-I is transferred to large, lipid-rich spherical HDL, a small part of the protein associates with small, protein-rich pre-beta HDL [86,115].

The main function of apoA-I removed from TGRLs upon their lipolysis appears to involve binding surface lipids released during this process. Surface TGRL remnants may thereby act as a sink for apoA-I, leading to the formation of HDL [93]. In addition, removal of apoA-I from TGRL can accelerate lipolysis as the protein inhibits lipolysis of

PC-containing triolein particles in vitro [135]. Finally, preferential binding of apoA-I to small TGRLs can delay lipolysis, retarding the LPL–apoC-II–triolein complex formation at the surface [136]; such binding can be facilitated by free fatty acids released during lipolysis. Yet another function of intestinally-derived apoA-I may include host protection from mesenteric inflammation, given the anti-inflammatory properties of the protein [2].

2.2.3.2. Role of CETP. CETP may play an inhibitory role towards cholesterol removal from TGRL upon lipolysis. Consistent with this hypothesis, torcetrapib, a specific CETP inhibitor, enhances the transfer of fluorescent FC to HDL upon TGRL lipolysis by LPL [114]. This effect can be explained by the capacity of CETP to transfer cholesterol, in a form of CE, from HDL back to TGRL [6]. When FC is transferred from TGRL to HDL and esterified under the action of LCAT, a molecule of CE formed becomes a substrate for CETP and can be readily transferred back to TGRL in exchange for a molecule of TGRL-derived TG (Fig. 1). In support of this mechanism, transfer of CE from HDL to VLDL is greatly enhanced when partially purified CETP is added to the mixture of VLDL, HDL and LPL [137]. Further along this line, transfer of LCAT-generated CE from HDL to VLDL is inhibited by a monoclonal antibody against CETP [138].

In addition to CE and TG, CETP can also transfer PL molecules [139]. The role of CETP in the postprandial transfer of PL is however controversial. Expression of human CETP in mice does not modify PL transfer to HDL during TGRL lipolysis in vitro [140]. By contrast, partial inhibition of CETP by an anti-CETP antibody reduces [^{14}C]-PL transfer to HDL upon lipolysis.

2.2.3.3. Role of LCAT. Acting in concert with CETP, LCAT can diminish cholesterol accumulation in HDL upon TGRL lipolysis. Indeed, LCAT inhibition increases accumulation of fluorescent FC in HDL incubated with TGRL and LPL [114], consistent with a multi-step mechanism of FC movement between HDL and TGRL upon LPL-induced lipolysis, according to which LCAT promotes removal of cholesterol from HDL, ensuring its transport back to TGRL (Fig. 1). Consistent with this view, LCAT inhibition during incubation of plasma with LPL in vitro decreases accumulation of CE in VLDL [141].

2.2.3.4. Role of PLTP. Transfer to HDL of VLDL-derived lipids can be promoted by PLTP upon lipolysis [110]. More specifically, PLTP can accelerate the transfer of phospholipid [142]. Indeed, both in vitro and in vivo experiments show that during TGRL lipolysis, FC and phospholipid are transferred from lipid emulsion to HDL by distinct mechanisms independently from each other and that PL transfer can be facilitated by plasma proteins [140]. Consistent with this data, addition of partially purified human PLTP and CETP to VLDL lipolysed by LPL in the presence of HDL under conditions of LCAT inhibition accelerates the transfer of PL, FC and apoE to HDL and reduces the transfer of CE, resulting in diminished accumulation of total cholesterol in HDL [99].

2.2.3.5. Role of albumin. Albumin can enhance FC movement through plasma by acting as a shuttle transferring FC to its acceptors [143]. Even though there are no specific binding sites for FC on albumin, the protein may function as a low-affinity, high-capacity cholesterol transporter. Acting through this mechanism, albumin can accelerate cellular cholesterol efflux to HDL [143]. It is plausible that albumin can similarly enhance FC transfer to HDL during TGRL lipolysis.

2.2.3.6. Role of HL. TGRL hydrolysis by LPL is followed by CETP-mediated accumulation in HDL of TG, which is subsequently hydrolysed by HL [119,144]. In addition to TG, HL hydrolyses HDL phospholipid, suggesting that the enzyme may remove phospholipid to render HDL a more efficient acceptor for phospholipid derived from TGRL.

2.2.3.7. Role of SR-BI. Both FC and phospholipid transferred from chylomicrons to HDL upon lipolysis are taken up by the liver [145]. SR-BI appears to play a central role in this process [146].

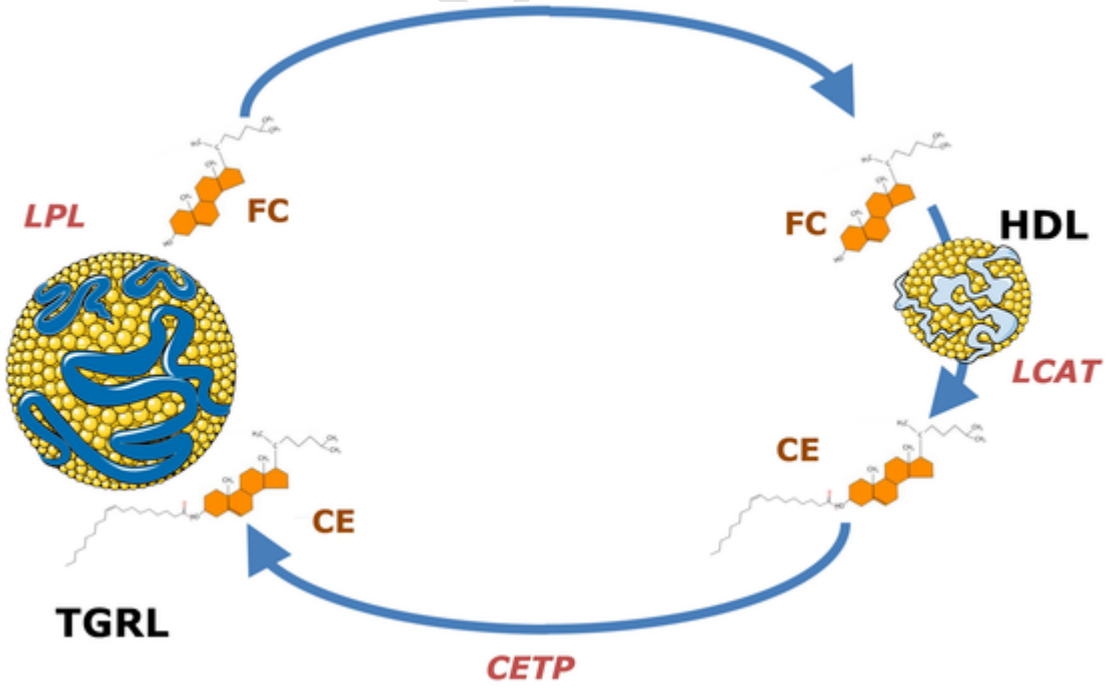

Fig. 1. Mechanisms of FC transfer to HDL upon TGRL lipolysis by LPL. TG lipolysis by LPL induces flux of FC and other surface components from TGRL to HDL. When FC is transferred from TGRL to HDL and esterified under the action of LCAT, a molecule of CE formed becomes a substrate for CETP and can be transferred back to TGRL in exchange for a molecule of TGRL-derived TG.

2.3. Function

2.3.1. The RRT hypothesis

Atherosclerosis can be considered as a natural postprandial phenomenon during which lipoproteins derived from the intestinal nutrient stream are retained and deposited in the arterial wall as a result of their phagocytosis in the intima by macrophages with a formation of foam cells [147–149]. Indeed, retention of cholesterol-rich, apoB-containing lipoproteins within the arterial wall is widely accepted to represent the key initiating event in atherogenesis [150]. In this concept, atherogenesis can be viewed as a common biological process and a direct consequence of food intake and energy production. In support of this view, recent epidemiological studies unequivocally demonstrate that elevated levels of not only LDL-C but equally those of postprandial TG and remnant cholesterol are independent risk factors for CVD [151].

To reduce atherosclerosis, the remnants must be cleared from the circulation as efficiently as possible. The presence of HDL accelerates TGRL lipolysis, removing lipids and proteins released from the surface of TGRL during this process [101]. Acquirement by HDL of surface components released upon TGRL lipolysis by LPL may therefore represent a key biological function of HDL aimed at facilitating TGRL catabolism and rapidly metabolising TGRL remnants [152]. As originally proposed by Chung et al., levels of HDL in plasma may affect the degree of dissociation of lipolytic surface remnants from the core remnants of TGRL by acting as an acceptor of surface remnants of TGRL [93,101].

The presence of HDL in lower vertebrates and its predominance among plasma lipoproteins in most species [73] indicates that HDL must play an important role in human and animal physiology from an evolutionary standpoint [43]. A central place of HDL in the postprandial lipid metabolism and energy production is consistent with the key biological role played by HDL. The atheroprotective function of HDL can thereby be secondary to its role in TGRL lipolysis. Indeed, HDL can indirectly reduce cholesterol influx in the arterial wall by removing from circulation cholesterol-rich atherogenic surface TGRL remnants [93]. Removal of the excess surface remnants can in turn reduce both the particle size and apoC content of core TGRL remnants, facilitating their hepatic uptake.

As a corollary, primarily surface, but also core, remnants can accumulate in the circulation when HDL levels are not high enough to accept all lipolytic surface fragments [93,101]. It can therefore be postulated that "one possible role of HDL in protecting against the development of atherosclerosis is its ability to prevent the accumulation of lipolytic surface remnants… in circulating blood" [101].

Acquirement by HDL of FC and other surface components of TGRL upon lipolysis can primarily be mediated by lipoprotein complexes containing apoA-I, the major HDL protein and potent biological detergent [123]. It is relevant in this regard that high amounts of apoA-I are synthesised by the intestine to be incorporated into chylomicrons and postprandially transferred to HDL [51]. ApoA-I can thereby ensure proper structure and function of HDL particles essential for shuttling excess surface lipids from TG-rich lipoproteins to the liver. However, the protein alone is probably not sufficient for the efficient FC removal from TGRL, suggesting that HDL particle as a whole should provide lipid surface required for the absorption of surface remnants [93,98,101]. Other structural HDL apolipoproteins, including apoA-II, apoE and apoM, can equally be expected to contribute to lipid transfer to HDL during lipolysis.

Taken together, these data led us to propose a reverse remnant-cholesterol transport (RRT) hypothesis [153] which involves acquirement by HDL of surface remnants of TGRL upon lipolysis with subsequent transport of remnant-derived FC to the liver in a pathway which originates in the intestine with the secretion of apoA-I and FC in chylomicrons followed by their transport to plasma via lymph for lipolysis in a postprandial state (Fig. 2). Transfer to HDL of surface remnants derived from lipolysed VLDL provides another contribution to this process, which can be active in a fasting state (Fig. 2). As a corollary,

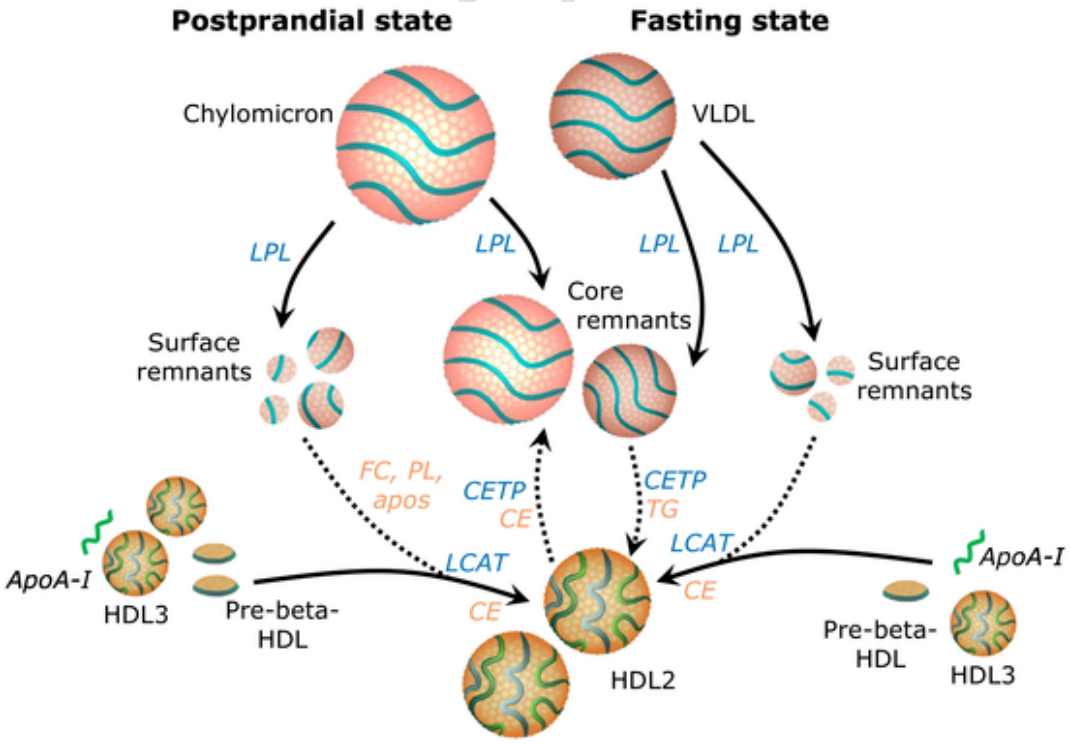

Fig. 2. Reverse remnant-cholesterol transport (RRT) pathway. In a postprandial state, chylomicrons are lipolysed by LPL to be converted into core and surface remnants. In a fasting state, VLDL is lipolysed by LPL to produce similarly TG-rich remnant particles. Surface TGRL remnants contain FC, PL and apolipoproteins (apos) which combine with the plasma HDL pool (primarily with lipid-poor, protein-rich subspecies), resulting in FC esterification by LCAT and HDL enlargement. HDL-derived CE produced by LCAT can be exchanged for TGRL-derived TG under the action of CETP. Lipoprotein components are shown in red, enzymes and lipid transfer proteins are in blue. Particle conversion and material transfer are shown as solid and dotted lines, respectively.

plasma concentration of HDL-C can represent an imperfect static measure of cholesterol flux through the RRT pathway. Indeed, steady-state concentrations of HDL-C, and particularly those of HDL2-C, were proposed to represent a biomarker of the removal of remnant TGRL cholesterol from plasma [154].

2.3.2. Impaired cholesterol flux from TGRL to HDL upon lipolysis

According to the RRT hypothesis, FC transfer from TGRL to HDL upon LPL-induced lipolysis should be impaired under metabolic conditions associated with CVD, including both low and extremely high HDL-C [14–16]. If this suggestion is correct, impaired FC transfer from TGRL to HDL upon lipolysis may underlie the non-linear relationship between HDL-C and CV risk [114].

2.3.2.1. Low HDL-C. Transfer of FC to HDL upon TGRL lipolysis by LPL can be diminished in low HDL-C patients with CVD and insulin resistance.

2.3.2.1.1. Myocardial infarction. Transfer of FC to HDL upon in vitro TGRL lipolysis by LPL is reduced in low HDL-C patients with acute myocardial infarction (AMI) [114]. Consistent with these data, fasting HDL-C and post-heparin LPL activity are reduced in survivors of AMI relative to matched controls, whereas postprandial TG response to fat load, chylomicron content of TG and apoB-48 and fasting apoB-100 are all elevated [152]. These data suggest that in AMI, low HDL-C can represent a marker of inefficient removal of TGRL remnants.

2.3.2.1.2. CAD. Postprandial increases in surface HDL lipids (FC and PL) are attenuated in CAD patients relative to controls [155]. In addition, the capacity of HDL to acquire FC under non-lipolytic conditions is reduced in CAD [156].

2.3.2.1.3. Insulin resistance. FC transfer to HDL upon TGRL lipolysis is decreased in low HDL-C patients with Type 2 diabetes [114]. In addition, FC transfer to HDL in the absence of TG lipolysis is reduced in patients with metabolic syndrome [156].

2.3.2.2. Genetically low HDL-C. Lipolytic FC transfer can be equally impaired under conditions of genetic HDL deficiency involving abnormal functioning of LPL, apoA-I ABCA1 and LCAT.

2.3.2.2.1. LPL deficiency. LPL deficiency is characterised by severe hypertriglyceridemia and low HDL-C. HDL content of FC and PL is reduced, while that of TG is elevated in patients with LPL deficiency [157]. HDL protein, apoA-I, apoCs and HDL-C are also reduced in cynomolgus monkeys following LPL inhibition by an anti-LPL antibody, while plasma TG are elevated [158]. In addition, LPL inhibition by an antibody in roosters reduces HDL content of cholesterol and phospholipid but increases that of TGs [159]. Together, these data strongly suggest that LPL deficiency impairs the transfer of FC and phospholipid from TGRL to HDL upon lipolysis.

2.3.2.2.2. ApoA-I deficiency. Postprandial TG response is markedly exaggerated in low HDL-C subjects with apoA-I deficiency caused by an autosomal apo A-I Q[-2]X mutation who feature premature CHD [160]. In addition, a frame-shift homozygote mutation in apoA-I resulting in the production of a shorter 26 kDa protein results in undetectable HDL-C in plasma and elevated TG [161].

Results of animal studies are consistent with the data obtained in humans. Thus, complete knockout of apoA-I in human apoB-transgenic mice results in decreased HDL-C levels which are paralleled by elevated TG [162]. Studies in mice further reveal that apoA-I directly links lipolytic FC transfer to postprandial atherogenesis. Indeed, aortic accumulation of [3H]-cholesterol upon fat load is highly elevated in low HDL-C apoA-I knock-out mice relative to both wild-type and apoA-I transgenic animals and is inversely associated with HDL-C [114]. In parallel, the capacity of murine HDL to acquire FC upon TGRL lipolysis by LPL is reduced in apoA-I knock-out mice, resulting in its negative correlation with the aortic accumulation of [3H]-cholesterol [114].

2.3.2.2.3. Deficiency. Fasting plasma TG levels are moderately elevated and postprandial TGs are highly elevated in homozygous patients with Tangier disease who present with non-detectable HDL-C levels [163]. Mechanisms potentially underlying hypertriglyceridemia in Tangier disease involve attenuated LPL activity, diminished TGRL hydrolysis [164], elevated VLDL secretion by the liver [165] and decreased CETP-mediated exchange of CE and TG between TGRL and HDL [163]. In addition, inadequate HDL maturation by ABCA1 as observed in patients with Tangier disease may lead to the reduction of plasma HDL pool below the threshold required for the efficient TGRL lipolysis, causing hypertriglyceridemia.

2.3.2.2.4. LCAT deficiency. When LCAT is deficient, both LCAT-mediated esterification of FC and hydrolysis of PL are impaired, resulting in the accumulation in plasma of lipoprotein X, large lipoprotein particle rich in FC and PL [166]. Such particles can also be produced in vitro upon VLDL perfusion through rat hearts [167]. As LCAT negatively affects FC transfer from TGRL to HDL upon lipolysis [114], the rate of this process can be expected to be normal in LCAT-deficient subjects despite their low levels of acceptor HDL particles. Such normal FC removal from TGRL upon lipolysis might contribute to the absence of elevated CV risk frequently observed in familial LCAT deficiency [25]. Interestingly, impaired LCAT activation by apoA-I can be a factor improving lipolytic FC transfer to HDL in apoA-I deficiency.

2.3.2.3. Extremely high HDL-C. FC transfer to HDL upon TGRL lipolysis in vitro is reduced in subjects with extremely high HDL-C levels of >100 mg/dl relative to healthy normolipidemic controls [114]. By contrast, the rate of this process is normal in subjects with high HDL-C of 70 to 100 mg/dl. Consistent with this observation, lipolytic FC transfer from TGRL to HDL is not compromised in high HDL-C, human apoA-I transgenic mice [114].

2.3.3. Determinants of FC transfer to HDL from TGRL upon lipolysis

Major factors determining the rate of the lipolytic FC transfer to HDL include concentrations of HDL and TGRL, activities of lipid transfer proteins, such as CETP and PLTP, and enzymes, such as LPL and LCAT, as well as intrinsic properties of lipoprotein particles (Fig. 3).

2.3.3.1. HDL levels. Dose-dependences of FC transfer to HDL upon TGRL lipolysis by LPL reveal direct relationship with HDL concentrations at low concentrations of HDL [114]. Such relationship most likely reflects the presence in the assay of increasing amounts of acceptor HDL particles for TGRL-derived FC. These data are consistent with accelerated transfer of [^{3}H]-cholesterol from VLDL to HDL upon their co-incubation under non-lipolytic conditions observed at increasing HDL concentrations [168]. Decreased FC transfer to HDL observed in low HDL-C patients with AMI and Type 2 diabetes may therefore reflect low concentrations of acceptor HDL particles [114] (Fig. 3). Indeed, FC transfer to AMI and control HDL did not differ in this study when the lipoproteins were compared on a protein concentration basis.

2.3.3.2. HDL particle profile. Small, dense, lipid-poor, protein-rich HDL particles display elevated capacity to acquire FC upon TGRL lipolysis by LPL as compared to large, light, lipid-rich, protein-poor HDL [114]. This observation agrees well with the potent capacity of small, dense HDL to efflux cellular cholesterol and to perform several other biological activities [9].

While relative concentrations of small, lipid-poor HDLs are elevated in low HDL-C subjects, high HDL-C states feature increased proportions of large, lipid-rich particles [169,170]. The superior capacity of small vs. large HDL to acquire FC upon TGRL lipolysis may therefore contribute to the reduced FC transfer to HDL observed in subjects with extremely high HDL-C levels [114] (Fig. 3).

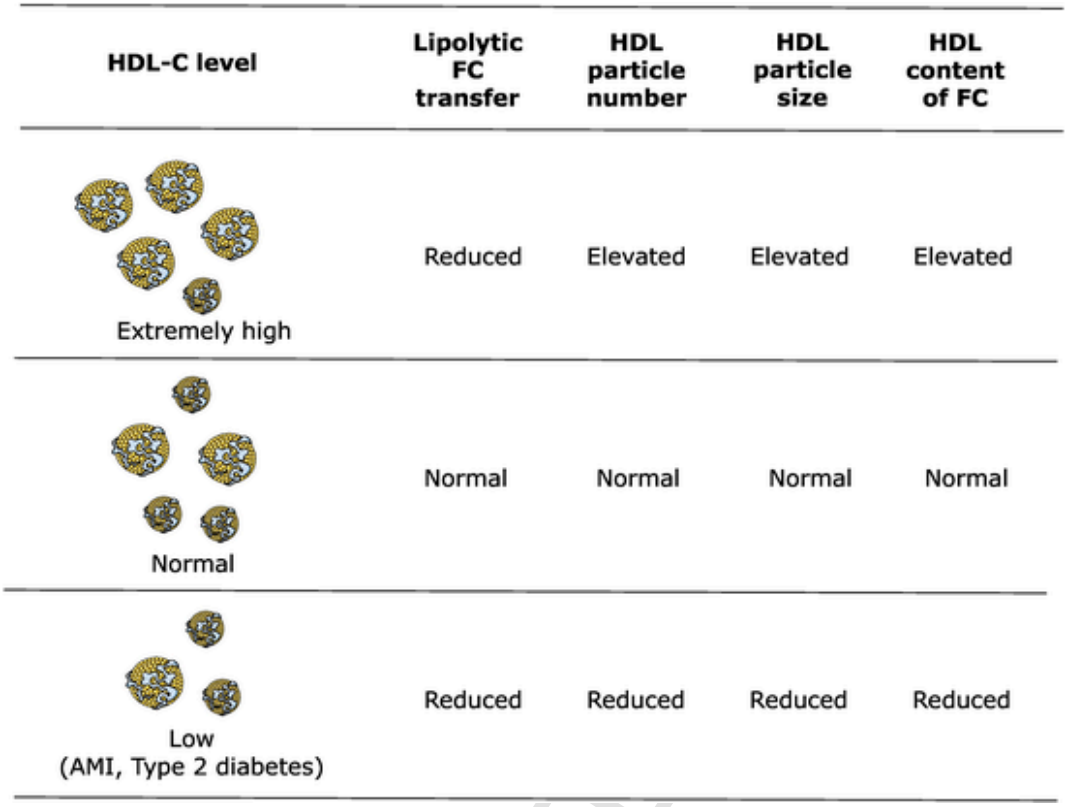

Fig. 3. Major determinants of FC accumulation in HDL upon TGRL lipolysis by LPL in low, normal and extremely high HDL-C states. The lipolytic FC accumulation in HDL is postulated to increase with increasing HDL particle number and to decrease with increasing HDL size and content of FC as well as with increasing CETP activity and LCAT activity.

2.3.3.3. HDL composition. HDL particles depleted of FC can be expected to acquire more FC as compared to those enriched in this lipid. Consistent with this notion, large, cholesterol-rich HDL particles, which predominate in subjects with extremely high HDL-C, may at some point become cholesterol donors instead of acceptors [171]. Furthermore, elevated FC/phospholipid ratio in HDL is capable of driving influx of FC from lipoproteins into cells [172]. Enrichment in FC might further contribute to the reduced capacity of HDL to acquire FC detected in subjects with extremely high HDL-C [114] (Fig. 3).

In contrast, diminished content of FC may contribute to the potent capacity of small, dense HDL3 to acquire FC from lipolysed TGRL. Indeed, FC content is decreased in small vs. large HDL [9] secondary to reduced solubility of FC in the boundary layer of PC adjacent to apoA-I as the proportion of such boundary lipids is inversely related to the HDL particle size [173].

2.3.3.4. Oxidative modification. Oxidative modification of apoA-I may exert deleterious effects on its function in TGRL lipolysis. Indeed, mild oxidation of Met residues alters secondary structure and decreases lipid affinity of apoA-I which becomes less capable of inducing formation of nascent HDL [174]. This process can be important for the removal of surface lipids upon TGRL lipolysis.

2.3.3.5. Lipid transfer proteins and enzymes. Lipid transfer proteins and enzymes actively participate in the transfer of surface lipids between TGRL and HDL during LPL-induced lipolysis. CETP appears to play an inhibitory role for cholesterol accumulation to HDL, which results from CETP-mediated transfer of cholesterol, in a form of CE, from HDL to TGRL [114] (Fig. 1). This process requires preliminary esterification of FC in HDL under the action of LCAT, consistent with an inhibitory role for this enzyme [114]. Elevated CETP activity typically observed in Type 2 diabetes and other types of atherogenic dyslipidemia [6] might therefore reduce FC accumulation in HDL upon lipolysis and impair clearance of TGRL remnants.

Furthermore, delayed CETP-mediated transfer of CE to VLDL from small, dense relative to large, light HDL [175] may contribute to the enhanced capacity of small, dense HDL to accumulate cholesterol upon TGRL lipolysis [114]. Finally, reduced FC accumulation in HDL detected in subjects with extremely high HDL-C levels may in part reflect elevated LCAT activity typical of this phenotype [48].

2.4. Therapeutic applications

The RRT hypothesis allows revisiting our view of therapies targeting HDL metabolism. Despite the failure of HDL-C-raising agents in patients treated by statins, not all HDL-C-raising mechanisms are doomed to fail. The outcome of these approaches should depend on the mechanism by which the HDL raising occurs and the effect on relevant HDL functions [176]. If removal from the circulation of atherogenic TGRL remnants does represent the principal biological function of HDL, therapies targeting HDL can be cardioprotective when they accelerate this process [101]. As a consequence, HDL-C-raising can be beneficial if it is derived from enhanced transfer of surface material, primarily FC, from TGRL to HDL upon LPL-induced lipolysis and is paralleled by reduced plasma levels of remnant cholesterol. The RRT hypothesis thereby put emphasise on diminishing cholesterol influx into arterial wall macrophages from remnant lipoprotein particles rather than enhancing cholesterol efflux from the macrophages as proposed by the RCT model.

Importantly, FC transferred to HDL upon TGRL lipolysis needs to be rapidly removed from the HDL pool to be excreted through the liver, either following esterification by LCAT or in an unesterified form [79]. If FC is accumulated in HDL, such HDL-C-raising will block the RRT pathway and can be considered excessive and not cardioprotective [27].

2.4.1. LPL activation

LPL activation can efficiently decrease plasma TG and raise HDL-C levels [159]. Acceleration of TGRL lipolysis by LPL largely underlies therapeutic effects of fibrates which raise HDL-C and reduce TG concentrations, potentially enhancing FC transfer through the RRT pathway.

The flux of TGRL-derived surface remnants, including cholesterol, through the HDL pool to the liver can equally be accelerated by the activation of adipocyte LPL. Indeed, activation of brown and beige adipocytes accelerates intravascular lipolysis, increases HDL-C, promotes HDL-C clearance and increases hepatic uptake of HDL by SR-BI, leading to atheroprotection [145].

2.4.2. Inhibition of apoC-III

Inhibition of apoC-III stimulates TGRL lipolysis by LPL, reduces plasma TG and raises HDL-C. These effects are observed when hepatic apoC-III production is inhibited by antisense oligonucleotides [177] or monoclonal antibodies [178]. Accelerated lipolysis, enhanced hepatic clearance of TGRLs and increased supply of their surface remnants to HDL can form a mechanistic basis of the effects of apoC-III inhibition.

2.4.3. Acceleration of apoA-I synthesis

From an epidemiological point of view, apoA-I may represent a more relevant therapeutic target than HDL-C [176]. As apoA-I concentrations in plasma are typically correlated with those of HDL-C, the U-shape epidemiology of HDL-C however warns against potentially deleterious consequences of excessive apoA-I-raising. Acceleration of hepatic synthesis of apoA-I might therefore bear a potential of reducing CVD primarily in patients with low apoA-I levels. Beneficial effects of apoA-I on lipid metabolism may involve efficient removal of surface lipids from TGRL undergoing lipolysis [136], together with acceleration of cellular cholesterol efflux and anti-inflammatory and antioxidative actions [179].

2.4.4. Statins

Statins appear to eliminate, or greatly reduce, therapeutic benefits of HDL-C-raising in the context of CVD [76]. Intriguingly, benefits of statins can be derived not only from LDL-C lowering but also from HDL-C-raising [180]. The latter effect predominantly arises from enhanced apoA-I production by the liver [181] and can potentially accelerate FC flux through the lipolytic pathway. Such enhancement of the lipolytic FC flux to HDL induced by statins may equally reflect elevated fluidity of the HDL surface monolayer, which facilitates HDL capacity to acquire lipids [182]. Indeed, statin treatment increases HDL content of polyunsaturated fatty acids (PUFAs) and decreases that of monounsaturated fatty acids (MUFAs) in rabbits, potentially increasing the surface fluidity [183].

3. Conclusions

The role of HDL in TGRL lipolysis and clearance from plasma of atherogenic remnant cholesterol as proposed in the framework of the RRT hypothesis [153] may prove useful for reconsidering our view of HDL metabolism. This new and well overlooked old function of HDL allows proposing explanation for some unexpected results of large-scale epidemiological studies and interventional trials. Indeed, the role of HDL in TGRL lipolysis links complex, non-linear U-shape relationships between HDL-C and CVD [14–16] to FC transfer to HDL upon TGRL lipolysis by LPL [114]. Furthermore, this HDL function may be helpful to understand why HDL-C-raising agents largely fail to produce clinical benefit in statin-treated patients. Finally, the RRT hypothesis provides an alternative point of view to critically reassess HDL-targeting therapies, switching attention to those focussing at LPL activation and apoA-I synthesis.

CRediT authorship contribution statement

Maryam Darabi: Methodology, Investigation, Writing.

Anatol Kontush: Conceptualization, Methodology, Resources, Writing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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