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Dysfunctional HDL in diabetes mellitus and its role in the pathogenesis of cardiovascular disease

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Abstract Coronary artery disease, the leading cause of death in the developed and developing countries, is prevalent in diabetes mellitus with 68% cardiovascular disease (CVD)-related mortality. Epidemiological studies suggested inverse correlation between HDL and CVD occurrence. Therefore, low HDL concentration observed in diabetic patients compared to non-diabetic individuals was thought to be one of the primary causes of increased risks of CVD. Efforts to raise HDL level via CETP inhibitors, Torcetrapib and Dalcetrapib, turned out to be disappointing in outcome studies despite substantial increases in HDL-C, suggesting that factors beyond HDL concentration may be responsible for the increased risks of CVD. Therefore, recent studies have focused more on HDL function than on HDL levels. The metabolic environment in diabetes mellitus condition such as hyperglycemia-induced advanced glycation end products, oxidative stress, and inflammation promote HDL dysfunction leading to greater risks of CVD. This review discusses dysfunctional HDL as one of the mechanisms of increased CVD risks in diabetes mellitus through adversely affecting components that support HDL function in cholesterol efflux and LDL oxidation. The dampening of reverse cholesterol transport, a key process that removes cholesterol from lipid-laden macrophages in the arterial wall, leads to increased risks of CVD in diabetic patients. Therapeutic approaches to keep diabetes under control may benefit patients from developing CVD.

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Introduction

High-density lipoprotein's role in cardiovascular disease

Coronary artery disease (CAD) remains the leading cause of death in the United States and many developed and developing countries [1]. While elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides are risk factors for developing coronary artery disease [2], the excessive accumulation of cholesterol by macrophages and subsequent conversion to foam cells [3, 4] sets the stage of atherosclerosis progression. Correlation of LDL-C to CAD necessitated statin therapy to prevent atherosclerosis, primarily by inhibiting HMG-CoA reductase, a key enzyme in the de novo cholesterol synthesis, and thereby leading to decreased serum LDL-C [2, 5, 6]. Low levels of high-density lipoprotein cholesterol (HDL-C) is another prominent risk factor for developing premature atherosclerosis [7]. Despite documented benefits of statins [2], a good proportion of individuals still remain at a higher risk of developing CAD [8]. At least in prior clinical studies, it was demonstrated that HDL-C levels inversely correlated with the risk of coronary artery diseases [8–11] as evidenced by clinical trial results [12–14].

The increasing incidence of diabetes worldwide and metabolic derangement and risk factors associated with this, leads to the development of cardiovascular disease (CVD) [15–17]. Among those, low HDL-C is characterized as one of the features of metabolic syndrome (MetS). The other risk factors include dyslipidemia,

hypertriglyceridemia, hypertension, and impaired glucose tolerance. A recent report suggests that MetS is becoming pandemic and the number of individuals suffering from MetS is likely to double by 2030 worldwide [18]. Therefore, aiming to correct dyslipidemia and increase HDL-C appeared to be a plausible therapeutic approach to reduce the risks of developing atherosclerotic lesion formation. Low HDL-C levels are the most common lipid abnormalities observed in men with CAD [11]. ApoA-I, the major protein component of HDL, determines the blood levels of HDL-C [19] and promotes cholesterol efflux, which in turn promotes reverse cholesterol transport. Therefore, raising HDL-C was thought to have protective effects against developing CAD. HDL's protective role occurs through inhibition of atherogenesis by promoting cholesterol efflux from peripheral tissues and from lipid-laden macrophages and arterial smooth muscle cells [20]. HDL also inhibits atherogenesis through other pathways like its direct effect on the vessel wall and inhibiting lipoprotein oxidation [21]. The most discussed atheroprotective function of HDL is enhancement of reverse cholesterol transport, a process in which HDL receives excess cholesterol from the peripheral tissues, including macrophages in the arterial wall, which is subsequently delivered to the liver for biliary excretion [19] (Fig. 1). The discovery of scavenger receptor-BI (SR-BI) [22, 23], ATP-binding cassette transporter A1 (ABCA1) [24, 25], and ATP-binding cassette transporter G1 (ABCG1) [26] have further added to our understanding of reverse cholesterol transport.

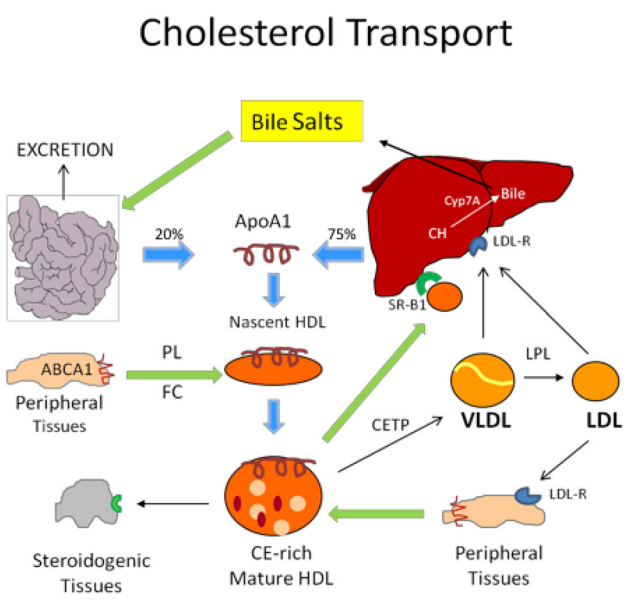

Fig. 1 Cholesterol transport. Apolipoprotein A-I, synthesized from the liver and the gut, forms nascent HDL particles. The nascent discoidal HDL particle accepts cholesterol and phospholipids from the peripheral tissues in ABCA1-dependent manner, and gets converted into cholesteryl ester-rich mature HDL particles. The mature HDL particles are then taken to the liver in a process called reverse cholesterol transport in which SR-B1 plays an important role in docking and accepting the cholesterol esters from HDL particles. The cholesterols delivered to the liver is converted into bile by cholesterol 7-α hydroxylase and excreted to the gut

Key roles of ABCA1 in HDL biogenesis, RCT, and atherosclerosis

A correlation between cholesterol efflux from macrophages and serum apoA1 concentration was first shown by Fournier et al. [27], which suggested a role of apoA-I in cellular cholesterol efflux. Later studies in a variety of cell-types showed that other apoproteins also function as cholesterol acceptors [28]. Marked induction in cholesterol efflux to acceptor lipid-poor apoA-I was observed in macrophages following treatment with cAMP [29, 30]. These observations together with other studies [31, 32] suggested the existence of an interaction between the acceptor apolipoproteins and the cell membrane component(s). In addition to HDL, other players such as SR-BI [23], ABCA1 [25], and hepatic lipase [33] have been shown to be part of the reverse cholesterol transport pathway.

Following the findings in WHAM chickens, the role of ABCA1 gained recognition in HDL biogenesis and reverse cholesterol transport and provided important insights into the correlation between cholesterol efflux and circulating HDL concentration [34]. In these mutant chickens, despite normal secretion rates of apoA-I, they have only 5% of the HDL compared to normal due to rapid catabolism of secreted apoA-I if not assembled into HDL particles. Subsequent studies confirmed the specific role of ABCA1 in the cellular cholesterol trafficking [35–37]. In the HDL biogenesis process, the discoidal lipid-poor apoA-I particle functions as a cholesterol acceptor and gets converted into spherical mature HDL particle, which then delivers this cholesterol to the liver and steroidogenic tissues via scavenger receptor class B type 1 (SR-B1)-mediated pathway (Fig. 1). ABCA1 participates in the reverse cholesterol transport by facilitating the efflux of cholesterol in an energy-dependent manner from cells to the acceptor lipid-poor apoA-I-particles (Fig. 2), which are then taken to the liver for excretion as bile salts. Despite other apoproteins being able to induce cholesterol efflux, lipid-poor apoA-I appears to be the preferred acceptor of ABCA1-mediated lipid efflux. Since apoA-I has been shown to specifically bind to ABCA1 [38], the lipid-poor apoA1 (preβ-HDL) functions as an acceptor of cholesterol and phospholipid in an ABCA1-dependent manner resulting the formation of mature cholesterol ester-rich spherical α-HDL particles following the action of LCAT [39]. SR-BI interacts with the mature α-HDL and facilitates the uptake of CE from the HDL particles (Fig. 2). Thus, any compromise in the

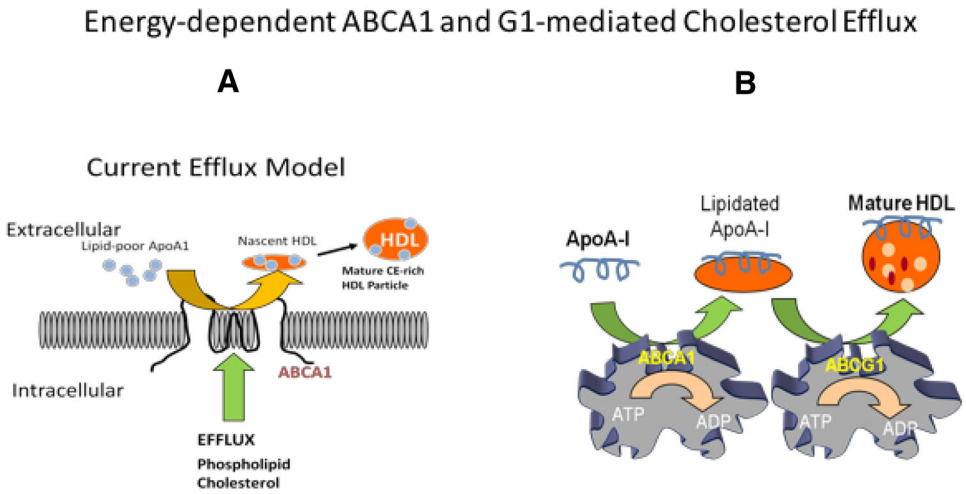

Fig. 2 **A** ABCA1-mediated cholesterol efflux. Lipid-poor discoidal HDL particle in the circulation accepts cholesterol and phospholipids from the tissues via ABCA1-mediated pathway. ABCA1 is a membrane protein that facilitates the transport of cholesterol and phospholipids from the tissues to the lipid-poor HDL particles and, as a result, the nascent HDL particles get converted into mature cholesterol ester-rich HDL particles capable of transporting cholesterol to the liver for excretion. Any defect in the membrane-associated ABCA1 protein renders them unable to mediate the cellular cholesterol efflux resulting into the deposition of cholesterol within the tissues. **B** ABCA1-and ABCG1-mediated cholesterol efflux requires energy in the two-step HDL maturation. Lipid-poor discoidal HDL particle in the circulation becomes lipidated by ABCA1using ATP followed by ATP-dependent maturation of HDL by ABCG1

function of HDL may lead to impaired cholesterol efflux leading to increased risk of CVD (Fig. 3).

Preβ-HDL particle formation and function

Pre β HDL fraction of HDL constitutes a heterogeneous population generated de novo by interaction between lipid-free apoA-I and ABCA1 [25] and these particles include lipid-free apoA-I to Apo-I-lipid complexes of varying sizes [40]. Thus, the only protein in the preβ-HDL is the apoA-I that has high affinity for lipids at its C-terminus that allows rapid association of apoA-I with phospholipids when preparing reconstituted HDL (rHDL) [41, 42]. The nascent phospholipid-apoA-I complex induces cholesterol efflux [43]. Depending upon the size of apoA-I-lipid complex, these particles are classified into preβ-HDL1 (smaller) and preβ-HDL2 (larger) particles [44]. As depicted in Fig. 2 the lipid-poor apoA-I generated through interaction with ABCA1gets more lipidated via ABCG1-mediated lipid efflux. The maturation of discoidal HDL particles into spherical HDL particles is carried out by LCAT-mediated esterification [39]. The smaller preβ-HDL, preβ1, with 1-2

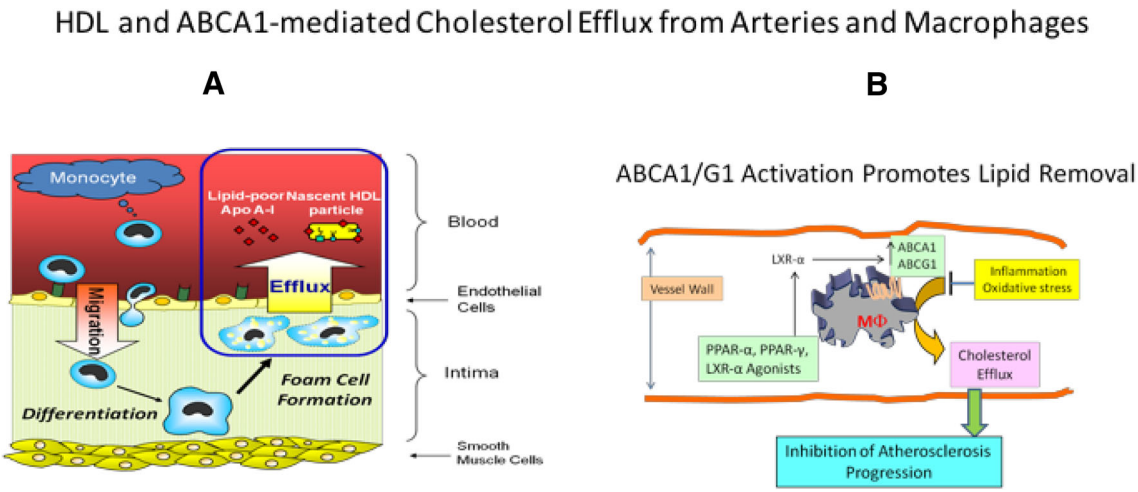

Fig. 3 Schematic representation of atheroprotective effects of ABCA1. **A** Lipid-laden macrophages in the arterial walls set the stage for the initiation of atherosclerosis via a variety of mechanisms. The removal of lipids from the macrophages is therefore a prerequisite in the process of inhibition of atherosclerosis. **B** ABCA1-inducing agents and stimuli accelerate the removal of cholesterol and phospholipids from the lipid-laden macrophages, and reduce the risk of predisposition to atherosclerosis

apoA-I per particle, is suggested to be more efficient in effluxing cholesterol from cells. The steady state level of preβ1 particles is emerging as a biomarker for the protective role of HDL and an independent indicator of CAD risk in humans [45]. Thus, the function and maturation of HDL is linked with the function of ABCA1 that lipidates lipid-poor apoA-I through cholesterol efflux and contributes to the reverse cholesterol transport pathway [46], suggesting that the formation and functionality of HDL is tightly linked to production of apoA-I and membrane-associated transporters, ABCA1 and G1 [47]. Any defect in these proteins lead to dysfunctional HDL [35, 48–50].

HDL's role in preventing LDL oxidation

While the main function of HDL that contributes to the atheroprotective property is its ability to efflux cholesterol from lipid-laden cells and arteries [20] (Fig. 3), the inhibition of LDL oxidation by HDL is another important property of HDL in attenuating progression of atherosclerosis [51]. Thus, HDL on one hand inhibits progression of atherosclerosis and on the other hand promotes plaque regression. HDL acquires antioxidative property by HDL-associated proteins such as paraoxonase I (PON1) and apoA-I. The association of apoA-I, CETP, LCAT, and PON1 has been shown to enhance HDL's ability to inhibit LDL oxidation [52, 53]. Among these associated proteins, PON1 appears to be the most important player in conferring antioxidant property to HDL particles to protect LDL from undergoing oxidation [54]. Myeloperoxidase (MPO) and PON1 are two key proteins in the promotion and prevention of LDL oxidation, respectively. While MPO is known to cause oxidative modification of lipoproteins [55, 56], PON1 prevents oxidation of lipoproteins [57, 58]. PON1 inhibits oxLDL-induced MCP1 formation by endothelial cells and MCP1 is known to induce recruitment of monocytes into the subendothelial space, a process that sets the stage for the initiation of atherogenesis. Attenuation of oxidative stress in macrophages by PON1 in transfected cells as well as in PON1 transgenic mice [59, 60] reduces atherosclerotic lesion formation [61], and PON1 deficiency was found to be associated with increased macrophage oxidative stress and atherosclerosis [62]. Thus, the ability of HDL to inhibit LDL oxidation appears to be largely dependent on the HDL-associated protein, PON1, which dampens the oxidative stress and confers LDL protection.

Elevated oxidative stress in diabetes mellitus causes oxidative modification of HDL particle and its main protein component, apoA-I, and contributes to the generation of dysfunctional HDL [56, 63–66]. Hyperglycemia in dyslipidemic non-diabetic individuals induces oxidative modification of HDL resulting in higher oxidized HDL [67]. HDL's antioxidant property is impaired in Type 1 diabetic individuals [68], suggesting a distinct role of high glucose in impairing HDL's function as an antioxidant. It is possible to restore HDL function by infusing the apoA-I mimetics, the main protein component of HDL [69]. Thus, the ratio of oxLDL to LDL and oxLDL to HDL are important in determining the risks for developing CVD. Indeed, Motamed et al. [70] determined in type 2 diabetes patients that both oxLDL/LDL and oxLDL/HDL are potent biomarkers for oxidative stress, and support earlier studies by Girona et al. [71] who showed that oxidized lipoprotein ratios are associated with atherosclerotic lesion formation in patients with diabetes. Thus, decreased HDL antioxidant capacity is important in atherosclerosis susceptibility [72]. Pathological and physiological conditions that strip off or decrease HDL-associated proteins, PON-1 [62], apoA-I [73–75], or LCAT [76, 77] have been shown to either decrease HDL or make them susceptible to oxidation.

Raising circulating HDL to promote reverse cholesterol transport and attenuate atherosclerosis progression

Epidemiological studies suggested that raising HDL may be beneficial in reducing the risk of CVD [14]. Several approaches have been tried to raise HDL, including CETP inhibition [78], LCAT activation [79, 80], and infusing nascent HDL particles to regress atheroma volume [81]. The very first CETP inhibitor, torcetrapib [82], despite showing massive increase in HDL concentration in ILLUMINATE clinical trial, did not show any benefit in outcome studies, possibly due to high aldosterone levels [83, 84]. Another class of CETP inhibitor, dalcetrapib that covalently binds to CETP, showed enhanced RCT in preclinical models, also failed to show positive results in cardiovascular outcome studies (dal-OUTOMES) [78]. While torcetrapib dampened endothelial function because of increased aldosterone [83], dalcetrapib increased CRP and thereby increased vascular inflammation [85]. These adverse effects may have resulted in lack of positive outcome. Macrophage-to-feces RCT involves ABCA1-dependent cholesterol efflux and may be considered as a RCT biomarker [86]. However, both elevation of CETP as well as absence of CETP increase RCT in this assay [87], thus making it difficult to interpret the data. Anacetrapib is being evaluated in REVEAL clinical trial and the results are expected to be announced in 2017 [78]. A potent and selective CETP inhibitor, evacetrapib, with no effect on aldosterone is being evaluated in ACCENTUATE trial for LDL reduction and in ACCELERATE trial in patients with high risk vascular disease [78]. Because these selective CETP inhibitors massively reduce LDL cholesterol, the

clinical data would require careful evaluation to determine contribution of HDL elevation in atheroprotection.

In order to avoid chemotype and class effect of small molecule CETP inhibitors, researchers have explored other approaches like CETP antibody [88] and siRNA [89], albeit only in the preclinical animal models, primarily to show proof-of-concept of these approaches. That the elevation of HDL may not necessarily impart all beneficial effects was demonstrated by mouse genetic models overexpressing SR-BI [90, 91] or lacking SR-BI [92]. Mice lacking SR-BI, although had elevated HDL levels, but showed decreased RCT in macrophage-to-feces assays and increased atherosclerosis [92, 93]. On the other hand, mice overexpressing SR-BI had lower HDL concentrations compared to WT littermates and exhibited higher RCT activity in MS-RCT assay and showed atherosclerosis attenuation [94, 95]. It was observed that HDL functionality was compromised in SR-BI knockout mice despite higher HDL concentration [96], suggesting that SR-BI is atheroprotective and lack of SR-BI while showed increased HDL, but appeared to be dysfunctional that contributed to lack of atheroprotection. Further support to this hypothesis comes from human genetic studies that identified a rare SR-BI variant with higher HDL concentration, but increased risks of coronary artery disease [97]. These findings are consistent with the notion that HDL function is more important than the HDL concentration and any factor that dampens HDL function may have negative effects on CVD outcome. It is quite possible that the lack of benefit in CVD outcome studies with RVX-208 [98] and CER-001 [99] may have to do with the compositional changes in HDL that influences HDL function in a way that does not translate into CVD benefits. RVX-208 is identified as a BET inhibitor [100] and in one study shown to influence glucose metabolism [101]. A clear mechanism of action of BET inhibitors in glucose production or excursion is likely to add further knowledge to our current understanding and to establish a meaningful link between BET inhibition and diabetes.

HDL modification in diabetes mellitus impacts reverse cholesterol transport

Individuals with diabetes have a greater risk of developing CVD compared to non-diabetic individuals since 2/3rd of CVD-related deaths occur in diabetic population [102]. At least 68% of people age 65 or older with diabetes die from some form of heart disease; and 16% die of stroke. Therefore, adults with diabetes are two to four times more likely to have heart disease or a stroke than adults without diabetes. Given the projected diabetes population worldwide and in the US in particular [103], even larger proportion of population appears to be at risk of developing CVD complications. Type 2 diabetes mellitus and the cluster of pathologies characteristics of metabolic syndrome including insulin resistance, obesity, and high plasma triglycerides are often associated with low HDL [104, 105], and renders them to become dysfunctional as a result of the formation of advanced glycation end products [104, 106–108]. Insulin resistance contributes to low HDL cholesterol, and low HDL may promote development of diabetes [109], predict the development of type 2 diabetes in prediabetics [110], and promote progression of glycemia in those with established T2DM [111]. Individuals who do intensive exercise tends to have high HDL and also show improved glucose tolerance [112], suggesting a link between low HDL and energy homeostasis. One of the risk factors of CVD is low level of HDL [8–11] as seen in individuals with diabetes [104, 105]. Therefore, individuals with diabetes would have higher risks of developing CVD [102] as a result of impaired reverse cholesterol transport through reduced cholesterol efflux capability [107, 113, 114]. Impairment in the RCT may increase CVD risk [115]. Indeed, Rohatgi et al. [116] investigated the cholesterol efflux capacity and its association with incidence of atherosclerotic CVD outcome in a large population cohort. These investigators not only measured the concentration of HDL and number of HDL particles, they also measured cholesterol efflux capacity at baseline in 2924 adults free from CVD from the Dallas Heart Study, a probability-based population sample. The primary endpoint was defined as a first non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization or death from cardiovascular causes, all grouped as atherosclerotic CVD, with a median follow-up period of 9.4 years. The cholesterol efflux capacity, a new biomarker that characterizes a key step in reverse cholesterol transport, was found to be inversely associated with the incidence of cardiovascular events in a population-based cohort. This finding showed the importance of HDL function above plasma HDL cholesterol concentration and received recognition as a surrogate biomarker for CAD risk [117]. Thus, a correlation between cholesterol efflux capability of the serum and incidence of CVD appears to exist. However, this needed to be validated in individuals with diabetes. Kubota et al. [118] carried out serum cholesterol efflux studies in individuals with glucose intolerance. An inverse correlation was found between the cholesterol efflux capability and extent of glucose intolerance in an oral glucose tolerance test in all subjects. Most notably, the serum cholesterol efflux capacity was significantly lower in subjects with glucose intolerance. This study established a link between glucose intolerance and cholesterol efflux and demonstrated that cholesterol efflux capacity is impaired in Japanese-Americans newly diagnosed with glucose

intolerance. As suggested [116], the impairment in cholesterol efflux capacity in these individuals may contribute to increased risk of atherosclerotic CVD.

One of the hallmarks of diabetes is increased glycation end products [119–122]. Since advanced glycation end products promote oxidative stress leading to oxidation of physiologically important biomolecules and increased inflammation, it is possible these biological attributes of glycated proteins in individuals with diabetes may impact the functionality of HDL. To address this, an elegant study was carried out by Mechado-Lima et al. [123]. Basically, these investigators isolated albumin from non-diabetes and type 1 diabetes mellitus individuals and treated J774 cells loaded with ^{3}H-Cholesterol followed by measurement of cholesterol efflux to the media apoA-I, HDL_3 or HDL_2. Simultaneously, they also measured intracellular ABCA1 protein content and a set of genes by real-time PCR. Both apoA-I and HDL_2-mediated cholesterol efflux were found to be impaired in macrophages treated with albumin isolated from diabetic patients compared with non-diabetic albumin-treated cells, which was attributed to intracellular ABCA1 protein content, demonstrating that the advanced glycated albumin isolated from poorly controlled type 1 diabetes mellitus patients alters macrophage gene expression impairing ABCA-1-mediated reverse cholesterol transport that possibly contributes to the increased risk of CVD in diabetic patients. A similar study by Traldi et al. [122] with glycated human serum albumin isolated from poorly controlled diabetic patients showed impairment of cholesterol efflux from macrophages. They treated mouse peritoneal macrophages with human serum albumin isolated from control, type 1 and type 2 diabetic subjects and measured gene expression related to cholesterol efflux as well as cholesterol efflux using J774 macrophages. ABCA-1 protein level and apoA-I mediated cholesterol efflux reduced by 50 and 60%, respectively, in macrophages exposed to HSA from type 1 and type 2 diabetic patients when compared to that exposed to HSA from control subjects. Thus, compromised RCT in diabetes mellitus contributes to atherosclerosis.

A comprehensive clinical study in 1745 diabetic patients and 1749 control patients from the EPIC- Norfolk study of 25,639 individuals were carried out by Saleheen et al. [124]. These investigators quantified cholesterol efflux capacity in 1745 individuals with reported incidence of coronary heart disease and 1749 individuals with no cardiovascular disorder by a widely accepted cholesterol efflux assay using J774 cells loaded with radiolabel cholesterol. Their studies showed a positive correlation of cholesterol efflux with both HDL-C as well as apoA-I, the main apoprotein of HDL that determines HDL concentration and to a great extent HDL function [19]. Interestingly, cholesterol efflux showed an inverse correlation with diabetes, a finding confirming earlier studies [118, 122, 123]. Additionally, cholesterol efflux capacity showed an inverse correlation with incidence of coronary heart disease events in this study [124], suggesting cholesterol efflux capacity of HDL as a predictor of coronary heart disease. A parallel study by Bao et al. [125] provided mechanistic insights into the correlation of cholesterol efflux capacity and type-2 diabetes mellitus. Along with serum cholesterol efflux, these researchers measured expression of CYP7A1, ABCG5, and LXR-beta in the peripheral blood monocytes by realtime PCR and Western blot. Out of 30 type-2 diabetes patients recruited in this study, half of them had complicated heart disease. Fifteen normal control individuals with no diabetes were recruited for comparison. Only CYP7A1 mRNA and protein showed correlation with the cholesterol efflux capacity. A significantly lower rate of macrophage cholesterol efflux was noticed in patients with type 2 diabetes compared to normal control subjects. Since a positive correlation between cholesterol efflux capacity and CYP7A1 existed, it was concluded that the reduction in cholesterol efflux capacity in type 2 diabetes patients is associated with the down-regulation of CYP7A1 expression.

To address impaired cholesterol efflux capacity in type 2 diabetic patients, a quite different approach was undertaken by Apro et al. [126]. These researchers isolated HDL from interstitial fluid as well as from peripheral plasma from type 2 diabetes patients ($n = 35$) and non-diabetic control individuals ($n = 35$). Both in normal control individuals as well as in diabetic patients, the cholesterol efflux assay showed lower efflux capacity in interstitial fluid as compared to the peripheral plasma. Whereas, plasma efflux capacity in type 2 diabetic patients were 10% lower compared to normal control individuals, the interstitial fluid cholesterol efflux capacity in type 2 diabetic patients showed a 28% reduction, suggesting that interstitial fluid cholesterol efflux capacity in type 2 diabetes mellitus is severely impaired and may contribute to their increased risk of CAD. In a mouse model of streptozotocin-induced diabetic nephropathy, Tsun et al. [127] studied the role of ABCG1 and SR-BI in renal cellular cholesterol efflux by evaluating expression of cholesterol transporters. In vitro studies established hyperglycemia-induced reduction in cholesterol transporters, ABCA1, G1, and SR-BI. Similar reduction in these three cholesterol transporters were observed in the kidney of streptozotocin-induced mouse model of diabetic nephropathy, suggesting that cholesterol efflux in kidney is compromised in type 1 diabetic conditions, leading to lipid accumulation in the kidney.

In terms of what makes HDL dysfunctional that dampens cholesterol efflux capacity, among other factors, post-translational modification of HDL has been suggested as one of them [128]. Although other posttranslational

modifications of HDL in diabetic patients have been noted [129], the oxidative modification of HDL particle and its main protein component, apoA-I, appears to be the primary cause of rendering HDL dysfunctional [56, 63–66]. Poor glycemic control in type-1 diabetes is associated with accelerated oxidative damage to apolipoprotein (apo) A-I [130] and advanced glycated albumin diminishes anti-inflammatory properties of HDL [131, 132]. Reconstituted HDL (rHDL) shows anti-inflammatory activity in humans [133–135]. ABCA1-mediated cholesterol efflux capability of HDL is compromised in type 2 diabetes patients [136], possibly caused by the oxidatively damaged apoA-I and increased inflammation [137, 138] (Fig. 4). Since antioxidative and anti-inflammatory properties of HDL are impaired in diabetics [138], this may contribute to HDL dysfunction [139]. HDL undergoes modification and multiple structural changes in an inflammatory environment and transforms normal functional HDL into "acute phase HDL" enriched in free fatty acids, triglycerides, serum amyloid A (SAA), and decrease anti-inflammatory enzymes, including paraoxanase [56, 64, 140–144]. In addition, inflammation induces secretion of myeloperoxidase (MPO), which has been shown to modify apolipoprotein A-I and impair its ability to accept cholesterol [64, 66, 142, 145–147]. MPO-mediated oxidation of apoA-I makes it proinflammatory [148]. Tryptophan substitution in apoA-I renders it resistance to MPO oxidation [149]. All these studies suggest that oxidative stress-induced HDL modification increases inflammation and contributes to HDL dysfunction.

Hyperglycemia causes increased flux through the polyol pathway, formation of advanced glycation end products, activation of protein kinase C isoforms, and increased hexosamine pathway flux, all of which may contribute to increased oxidative stress [150–152]. Excessive free fatty acids delivered to nonadipose tissues can lead to reactive oxygen species (ROS) formation through a number of pathways, including oxidative phosphorylation, activation of NADPH oxidase, and alterations in mitochondrial structure leading to ROS production [153–155]. In addition to evidence for activation of these pathways in cultured endothelial cells, human studies support the notion of increased systemic oxidative stress in diabetic subjects in whom increased circulating levels of adhesion molecules and oxidized lipids correlate with increases in HbA1c and hypertriglyceridemia [156]. The effects of oxidative stress in diabetes on both the vascular wall and lipoproteins in the circulation may promote atherogenesis. Jaleel et al. [130] provided intriguing evidence that poor glycemic control in type-1 diabetes is associated with accelerated oxidative

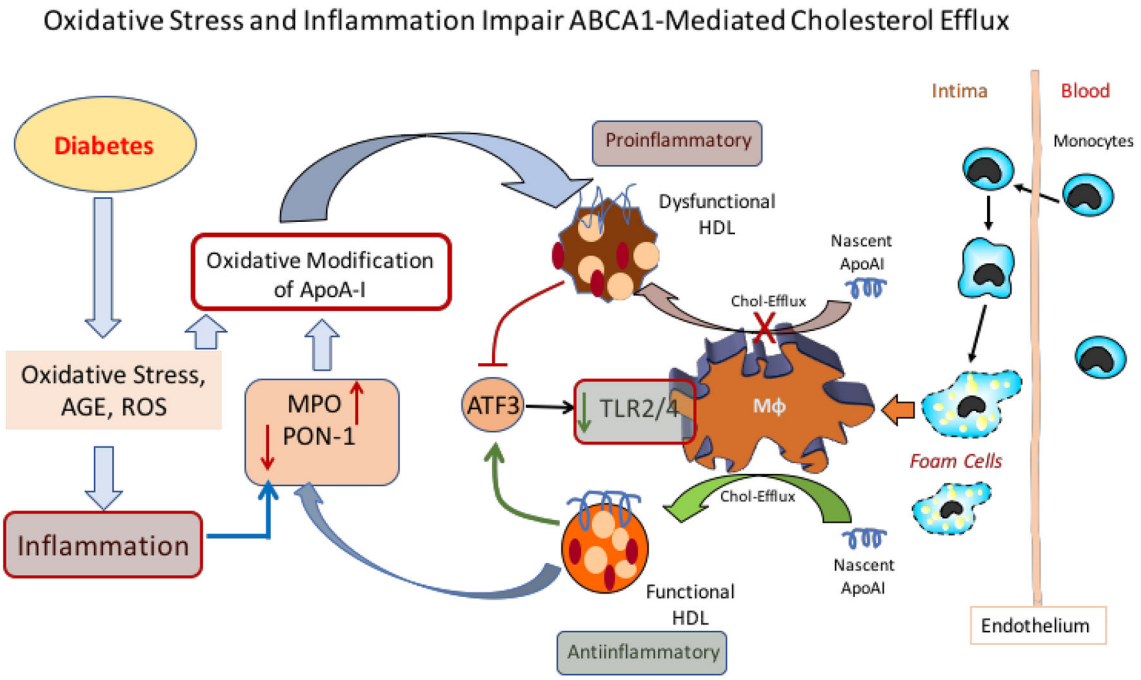

Fig. 4 Oxidative stress and inflammation impair reverse cholesterol transport in DM. Advanced glycation products and reactive oxygen species together with inflammation in DM induce MPO and decrease PON1 leading to oxidative modification of the main protein component of HDL, apoA-I. The resulting dysfunctional and proinflammatory HDL impacts immune response in macrophages through TLR2/4 by repressing the transcription factor ATF3, and impairs ABCA1-mediated cholesterol efflux leading to cholesterol accumulation and oxidation within macrophages entrapped in the subendothelial space. Additionally, oxidative environment in DM induces acute phase proteins like haptoglobin and CRP leading to impaired RCT and increased vascular inflammation that promote lipid deposition in arterial wall

damage to apoA-I. These investigators labeled newly synthesized proteins with ^{13}C-phenylalanine in human subjects and analyzed various plasma apoA-I isoforms by two-dimensional gel separation and mass spectrometry. Newly synthesized forms of the protein containing the propeptide and in more mature cleaved forms were analyzed. The older forms of apoA-I accumulated significantly more, suggesting damage of apoA-I as a result of a variety of reactions, including deamidation, oxidation, and carbonylation of amino acids that likely contribute to their altered migration in isoelectric focusing.

Given that apoA-I is a major component of HDL that protects against atherosclerosis by facilitating the removal of cholesterol from macrophages in the arterial wall, oxidative damage of apoA-I [130] may impair HDL function. Indeed, recent studies demonstrated the presence of significant amounts of oxidation products of apoA-I in human atherosclerotic plaques [142, 157]. Additionally, Kataoka et al. [158] showed that myeloperoxidase enzyme that participates in the oxidation of apoA-I, predict accelerated progression of atherosclerosis in diabetics. Similarly, Shao et al. [159] quantified site-specific oxidation of apoA-I and measured cholesterol efflux in the HDL isolated from control subjects as well as subjects with stable coronary artery disease or acute coronary syndrome. The two groups of patients, CAD and ACS, had higher levels of chlorinated tyrosine 192 and oxidized methionine 148 compared to control subjects, clearly pointing to the importance of oxidatively damaged apoA-I in rendering HDL dysfunctional (Fig. 4). Interestingly, these researchers found no differences in the MPO level between the groups. Subjects with CAD and ACS showed less cholesterol efflux capacity compared to control group. The concentration of chlorinated tyrosine 192 and oxidized methionine 148 was inversely correlated to ABCA1-mediated cholesterol efflux capacity and positively with the extent of atherosclerosis. This suggests that chlorinated tyrosine and oxidized methionine in circulating HDL may serve as a useful marker of the atherosclerotic CVD. Thus, these studies provide mechanistic insight into the etiology of the oxidative modification of apoA-I, and how the functionality of HDL is linked to increased cardiovascular risks in diabetes. Lu et al. [160] extended this work in diabetic patients and showed that the levels of apoA-I nitration and chlorination were increased, and apoA-I concentrations as well as cholesterol efflux activity were significantly decreased. Specifically, they showed that Tyr 192 was the major nitration and chlorination site in apoA-I from diabetic serum. In addition to decreased cholesterol efflux capacity in patients with diabetes, these investigators further showed loss of antiapoptotic properties of lipoproteins. These findings were corroborated by a recent study by Chen et al. [161] who measured nitrated-apoA-I (NT-apoA-I) in 777 patients with CAD. Additionally, they measured cholesterol efflux capacity in diabetic ($n = 327$) and non-diabetic ($n = 450$) individuals. Higher ratio of NT-apoA-I/apoA-I in diabetic patients suggested higher oxidative stress. Indeed, thiobarbituric acid-reactive substances and c-reactive protein levels in diabetes mellitus were independent predictors of elevated NT-apoA-I/apoA-I ratio. Thus, oxidative stress in patients with diabetes leading to oxidative modification of apoA-I renders HDL dysfunctional in carrying out cholesterol efflux function, thus linking dampened cholesterol efflux to coronary artery disease risk in diabetic patients (Figs. 3, 4).

HDL and apoA-I modulate AMPK function and reverse cholesterol transport

Given the higher prevalence of cardiovascular morbidity and mortality in diabetics, this is an important area to pay attention to. Recent cell-based studies suggest that HDL may modulate plasma glucose through both insulin-dependent [162, 163] and -independent and AMPK-mediated mechanisms [164]. The ATP-binding cassette transporter A1 (ABCA1) has been shown to modulate insulin secretion [163], and HDL can reverse the deleterious effects of oxidized low-density lipoprotein (LDL) on insulin secretion by pancreatic beta cells [162]. In addition, HDL may also increase glucose disposal through direct effects in skeletal muscle, the major site of glucose disposal in the body. It was reported that HDL and apoA-I activate the key metabolic regulatory enzyme AMP-activated protein kinase (AMPK) in endothelial cells and are critical for the nitric oxide-mediated vasodilatory effects of HDL [165]. Infusion studies with recombinant and reconstituted HDL (rHDL) demonstrated modest effects on coronary plaque morphology and volume [166, 167] and also showed improved endothelial function in type 2 diabetes mellitus [168].

Diabetic individuals often have higher non-esterified fatty acids that may impact ABCA1-mediated cholesterol efflux. Indeed, unsaturated fatty acids inhibit ABCA1-mediated cholesterol efflux [169]. Given the elevated levels of fatty acids in diabetics [170], this finding is relevant in explaining, at least in part, the dampening of cholesterol efflux capability in diabetic individuals. This together with enhanced apoB secretion by fatty acids as a result of impaired presecretory degradation of apoB [171–173] contributes to the CVD risks in diabetic individuals [124, 174–176]. It therefore appears that ABCA1 could be important not only in the inhibition of progression of atherosclerosis [25, 34, 177–179], but also in metabolic diseases [136]. Wang and Oram [169] studied the effects of fatty acids, ranging in carbon chain length from 8 to 20, on cholesterol and phospholipid efflux in murine J774 and RAW 264.7 cells. The saturated fatty acids, palmitate and

stearate, neither inhibited ABCA1-mediated cholesterol and phospholipid efflux nor they influenced ABCA1 protein. However, unsaturated fatty acids, oleate and linoleate, reduced cholesterol efflux as well as ABCA1 protein in a dose-dependent manner. Interestingly, oleate and stearate did not alter ABCA1 mRNA. As determined from ABCA1 turnover studies, it was concluded that unsaturated fatty acids enhanced the degradation of ABCA1 protein. These authors investigated the mechanism of fatty acid-mediated degradation of ABCA1 and carried out elegant studies to demonstrate that unsaturated fatty acids phosphorylate and destabilize ABCA1 through a phospholipase D2 pathway [180]. Further studies revealed that protein kinase C delta pathway is also involved in this process [181]. Thus, it appears that the triggering of the ABCA1 degradation by fatty acids possibly occurs via a mechanism distinct from the one observed with the cAMP withdrawal [38].

Although the role of AMPK in attenuating diabetes through glucose catabolism and energy balance has been well studied [182–184], the role of apoA-I on energy and glucose metabolism was first investigated by Han et al. [164] in C2C12 myocytes. These investigators reported AMPK phosphorylation at Thr-172 following treatments with apoA-I, and this effect was found to be specific to apoA-I protein since treatment with apoB did not result into AMPK phosphorylation. ApoA-I also increased glucose uptake by C2C12 cells like AMPK activators [185]. These effects were similar to AMPK activation by adiponectin, leading to increased glucose uptake [186]. Extension of this study in apoA-I$^{-/-}$ mice further supported the hypothesis that apoA-I is involved in glucose and energy metabolism, since apoA-I$^{-/-}$ mice had higher circulating glucose and impaired glucose tolerance compared to the WT littermates; increased HDL in apoA-I Tg mice provided protection against diet-induced hyperglycemia through increased glucose catabolism [187]. Based on these findings, Drew et al. [109] extended these studies in human primary skeletal muscle cells isolated from type 2 diabetic patients infused with either a placebo or reconstituted HDL. There were reductions in the fasting glucose in the rHDL treated group compared to the placebo group. In cultured primary human skeletal muscle cells, apoA-I increased glucose uptake by 50%, which was associated with the activation of AMPK as measured by the AMPK phosphorylation at Thr-172. To further gain insights into the mechanism of apoA-I/HDL-mediated AMPK activation, these investigators examined two primary pathways of AMPK activation, i.e. LKB1 and CaMKK, the two upstream kinases known to phosphorylate AMPK [184, 188, 189]. They found that HDL-mediated induction of AMPK phosphorylation occurs via CaMKK-mediated pathway, since the CaMKK inhibitor STO609 abolished HDL-mediated phosphorylation of AMPK. Interestingly, the HDL-mediated induction of skeletal muscle glucose uptake occurred in ABCA1-dependent manner, since ABCA1 blocking antibody inhibited apoA-I and HDL-mediated uptake of glucose [109].

Low-grade inflammation in diabetes impairs reverse cholesterol transport

Atherosclerosis has been characterized as a chronic inflammatory response to LDL oxidation and deposition in arteries, but the mechanisms linking cholesterol accumulation in macrophage foam cells to inflammation are not completely understood. One of the mechanisms to protect cells from free cholesterol and oxysterol-induced toxicity during progression of atherosclerosis is the macrophage cholesterol efflux [86, 94, 190, 191]. During the cholesterol efflux process, the ATP-binding cassette transporters ABCA1 and ABCG1 are important players responsible for the major part of macrophage cholesterol efflux to HDL in macrophage foam cells [192]. Recent studies have shown that the sterol efflux activities of ABCA1 and ABCG1 modulate macrophage expression of inflammatory cytokines and chemokines as well as lymphocyte proliferative responses [193, 194]. Accumulating evidence suggests that by promoting cholesterol and oxysterol efflux, HDL regulates all these cellular responses in macrophage foam cells [192]. Indeed, several studies demonstrated that native and reconstituted HDL, apoA-I and apoA-I mimetic peptides, all show anti-inflammatory activity [133, 135, 195–198]. Inflammation modulates HDL composition and function [196, 199] and impairs reverse cholesterol transport [139, 200], and infusion of reconstituted HDL during human endotoxemia exerts anti-inflammatory activity [133]. Thus, native apoA-I and HDL-C show anti-inflammatory activities leading to enhancement in reverse cholesterol transport [201]. Indeed, increased inflammation was observed in mice lacking apoA-I [202], suggesting the role of apoA-I as an anti-inflammatory agent. Thus, accumulating evidence suggests an anti-inflammatory role for native unmodified HDL, but becomes inflammatory when it undergoes modifications [148] (Figs. 4, 5).

Two proteins, ABCA1 and ABCG1, important in reverse cholesterol transport play distinct roles in macrophages immune response. In macrophages lacking ABCA1 or ABCG1, TLR4 cell surface expression increased, albeit ABCG1 deficiency showed greater macrophage inflammatory response compared to ABCA1 deficiency [203]. These studies demonstrate that the primary function of HDL and ABC transporters in cholesterol efflux and reverse cholesterol transport are linked to anti-inflammatory and immunosuppressive functions of HDL. A recent study [204] demonstrates that dysfunctional HDL from patients with chronic kidney dysfunction (CKD) showed

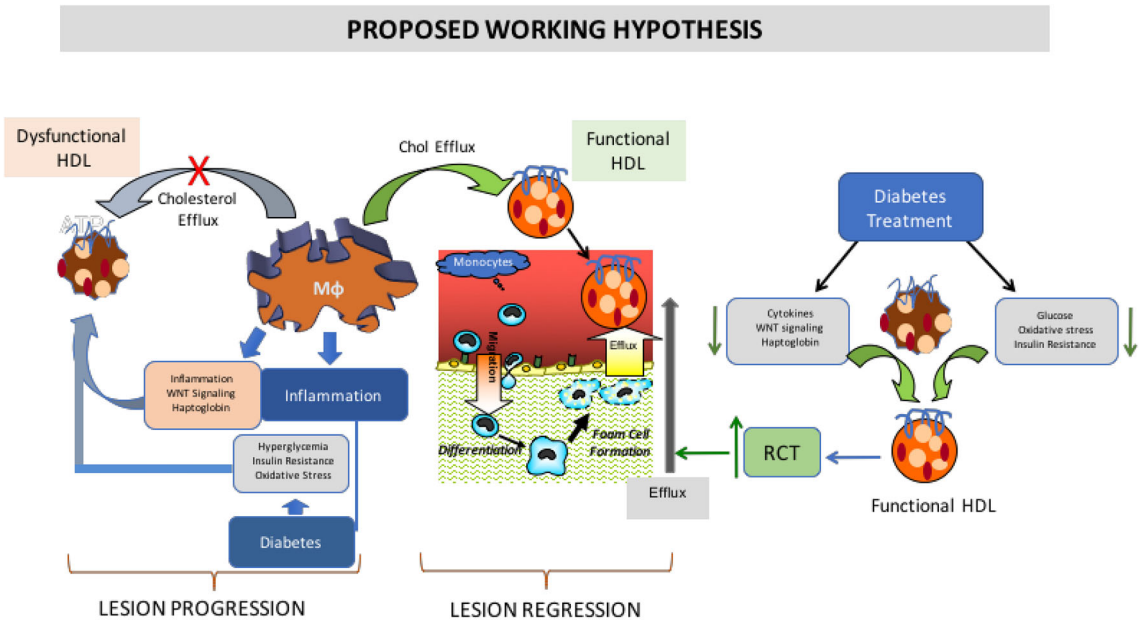

Fig. 5 Proposed working hypothesis. The biologic sequence of events that leads to HDL dysfunction is shown here. HDL performs its normal function by removing cholesterol from lipid-laden macrophages in the arterial wall, thus causing lesion regression. In diabetic mellitus, high oxidative environment causes inflammation in macrophages entrapped in the subendothelial space resulting in the secretion of proinflammatory cytokines and acute phase proteins like haptoglobin and CRP. The dysfunctional HDL impairs cholesterol efflux from lipid-laden macrophages. Treatment with antidiabetic drugs attenuates hyperglycemia which in turn reduces AGE, oxidative stress, and inflammation, and makes HDL functional and capable of promoting cholesterol efflux. This results in attenuating vascular inflammation leading to atherosclerotic plaque regression

unfavorable physiological functions by increasing superoxide dismutase production and reducing NO. These unfavorable activities were found to be occurring through toll-like receptor-2/4 (TLR-2/4). The HDL isolated from healthy counterpart did not show these unfavorable activities. Thus, the anti-inflammatory properties of HDL is linked to immune response through a number of mechanisms [205, 206], leading to suppression of Toll-like receptor 2 (TLR2) signaling [207] and suggesting that the HDL-mediated cholesterol efflux inhibits cellular inflammatory signaling, including inhibition of MCP-1 expression, a key player in monocyte transmigration. The molecular mechanisms of how HDL can modulate inflammation, particularly in immune cells such as macrophages, were investigated by De Nardo et al. [208]. These researchers found that the transcriptional regulator ATF3 in macrophages downregulates the expression of Toll-like receptor (TLR)-induced proinflammatory cytokines in an HDL-dependent manner, since the protective effects of HDL against TLR-induced inflammation were entirely dependent on ATF3. In LPS-induced animal model, Dandekar et al. [209] demonstrated the role of cAMP-responsive element-binding protein hepatic-specific (CREBH) and TNF receptor-associated factor 6 (TRAF6) in mediating TLR signaling in HDL-dependent manner, suggesting a mechanism of how HDL is involved in inflammation through toll-like receptors. These findings may explain the broad anti-inflammatory and metabolic actions of HDL and provide the basis for predicting the success of new HDL-based therapies.

Lipid raft in the plasma membrane appears to be a key regulator of macrophage inflammation, since one of the mechanisms of enhanced inflammatory responses in ABCA1 or ABCG1 deficiency appears to be through increased lipid raft formation in macrophages [210–213]. That cholesterol efflux is linked to immune response in ABCA1 or ABCG1 deficient macrophages was further demonstrated by treatment with cyclodextrin that removes cholesterol and attenuates inflammatory response. It was shown [212] that the modulation of membrane cholesterol by cholesterol efflux in ABCA1 or ABCG1 deficiency increased TLR4 cell surface expression.

Recent studies by Bensinger et al. [214] reported that Liver X Receptor (LXR) signaling, that promotes cholesterol efflux via ABCA1 and G1 stimulation, is involved in T-cell lymphocyte proliferation in an ABCG1-dependent fashion. Mice lacking apoA-I, an important component of cholesterol efflux, also stimulates T-cell proliferation and activation and some features of autoimmunity when backcrossed into an LDL receptor-deficient background [215]. These studies strongly suggest that HDL-mediated cholesterol efflux via LXR-regulated ABC transporters plays a key role in dampening lymphocyte proliferation and activation. Regulatory T cells (Tregs) express SR-B1

[216], which facilitates the uptake of HDL from microenvironment. A recent study demonstrates that LDL is not taken up by Treg, and HDL-derived fatty acids serve as fuel for the survival of Tregs [217]. Additionally, these authors further showed that mitochondrial activity was increased in the Tregs that internalized HDL, but not those that did not [217]. Thus, HDL plays an important role in the survival of Tregs, leading to the suppression of proatherogenic effector T cells [218].

To confirm if HDL function is compromised in inflammatory disease, Charles-Schoeman et al. [219] isolated HDL from 40 patients with Rheumatoid Arthritis patients and 40 age and sex matched healthy controls, and found that cholesterol efflux, HDL's antioxidant function, and paraoxanase-1 (PON-1) activity in RA patients with high disease activity had significantly decreased ability to promote cholesterol efflux compared to HDL from patients with very low disease activity. This was further substantiated by the findings that there was higher plasma MPO activity in patients with dysfunctional HDL. Additionally, cholesterol efflux activity of HDL correlated significantly with its antioxidant activity.

Another study was carried out by Field et al. [220] in patients with Crohn's disease, which is a tumor necrosis factor-alpha (TNF-alpha)-driven gastrointestinal tract chronic inflammatory condition. These investigators reported dampened basolateral efflux of cholesterol to apolipoprotein A1 (apoA1) through TNF-alpha mediated decreases in HDL cholesterol levels by modulating the expression of intestinal ABCA1 and cholesterol efflux to apoA1. A different approach was pursued by de la Llera Moya et al. [199] to assess the effect of inflammation on HDL and RCT related parameters. They employed low-dose human endotoxemia that induces HDL remodeling through depletion of pre-beta1 HDL particles. Endotoxemia resulted in reduced capacity of HDL to efflux cholesterol. The HDL fraction, isolated following endotoxemia, had reduced capacity to efflux cholesterol in vitro from SR-BI and ABCA1, but not ABCG1 transporter cell models. Thus, inflammatory conditions lead to dysfunctional HDL. Autoimmune disease, systemic lupus erythematosus (SLE), patients have elevated inflammation and have a higher prevalence of subclinical atherosclerosis and higher risk of CV events. The factors causing cardiovascular risks in these patients were investigated by Ammirati et al. [221]. They found that among CV risk factors, only the two important players in the cholesterol efflux, HDL level and ABCA1-dependent cholesterol efflux capability, were markedly reduced, whereas the common carotid artery intima-media thickness (CCA-IMT) significantly increased in SLE patients compared to controls. These and other findings discussed above suggest that reduction in RCT capability, as a result of dysfunctional HDL or ABC transporters, in inflammatory conditions lead to impaired cholesterol efflux and increased risk of CV. In diabetic patients, both oxidative stress and inflammation are elevated that lead to HDL modification and impairs RCT function leading to increased risks of CVD.

HDL-associated proinflammatory protein, haptoglobin, is associated with diabetic atherosclerosis

Haptoglobin (Hp) is an acute phase hemoglobin (Hb) binding serum protein primarily synthesized in the liver [222–224]. Hp binds to free Hb in the serum and forms Hp/Hb complex. The endocytosis of this Hp/Hb complex by monocyte-macrophages is mediated by the scavenger receptor CD163 [225, 226]. The main function of haptoglobin is in infection and inflammation, where it acts as a natural antagonist for receptor-ligand activation of the immune system [224]. The level of haptoglobin increases in proinflammatory conditions [224, 227]. It is now well established that HDL function is impaired in proinflammatory conditions [133, 139, 202, 228]. Both the anti-inflammatory properties as well as the cholesterol efflux capabilities of HDL are significantly dampened [193, 229]. Increased levels of haptoglobin in proinflammatory condition preferentially associates with proinflammatory HDL in animal models as well as in humans [230, 231]. Elevated level of haptoglobin has been observed in humans with CVD [232–234], and HDL isolated from mice lacking this protein show anti-inflammatory activity compared to WT mice [231]. These findings together with the observations that the endocytosis of Hp/Hb complex [235, 236] is mediated by a receptor, CD163, exclusively expressed in the macrophages [225, 226], and the involvement of macrophages and inflammatory cytokines in the progression of atherosclerosis [237], suggest a potential role of Hp in macrophage cholesterol efflux and the progression of atherosclerosis [238–240]. Indeed, HDL-raising agent in apoE-deficient mice decreases haptoglobin, which was associated with attenuation of aortic lipid deposition [241]. Several studies carried out in diabetic patients with CVD show a strong association between diabetic CVD and haptoglobin [233, 234].

Hp gene exists as Hp-1 and Hp-2 alleles and the phenotypes show important molecular heterogeneity. In individuals with DM, the Hp2-2 genotype is suggested as a contributor for increased cardiovascular events compared with Hp1-1 or Hp2-1 genotype [233, 234]. Indeed, haptoglobin genotype was found to be associated with compromised reverse cholesterol transport in Hp2 diabetic mice because of increased oxidative stress [242]. Levy et al. [234] tested this hypothesis in a case–control sample from the Strong Heart study, a population-based

longitudinal study of CVD in American Indians. These investigators determined haptoglobin phenotype in 206 CVD cases and 206 matched controls and followed-up for 6 years. In multivariate analyses, DM patients with haptoglobin phenotype were highly statistically significant and independent predictor of CVD. The odds ratio of having CVD in DM with the haptoglobin 2-2 phenotype was found to be 5.0 times greater than in DM with the haptoglobin 1-1 phenotype. An intermediate risk of CVD was associated with the haptoglobin 2-1 phenotype. In another study, Lioupis et al. [243] investigated iron burden of carotid atherosclerotic plaques removed from patients treated for carotid disease and examined correlation with haptoglobin genotype and common cardiovascular risk factors. Twenty seven plaques from diabetic patients (16 with the Hp 1-1 or 2-1 genotype and 11 with the Hp 2-2 genotype) and 43 plaques from non-diabetic patients (20 with the Hp 1-1 or 2-1 genotype and 23 with the Hp 2-2 genotype) were evaluated. They found that the density of Perl's iron stain was significantly higher in plaques from diabetic patients with the Hp 2-2 group compared with that in the Hp 1-1 or 2-1 group. The correlation and regression analysis of all possible clinical and laboratory predictors of intraplaque iron deposition showed that four factors were independently associated with intraplaque iron deposition; these were male gender, serum homocysteine, Hp 2-2 genotype and diabetes mellitus treatment. To further corroborate the relation between Hp genotype and CV risks in DM, Purushothaman et al. [244] carried an elegant study in 40 diabetic patients. These patients were genotyped for haptoglobin allele, Hp-1 and Hp-2 and after atherectomy, several parameters like plaque hemorrhage, hemoglobin-binding protein, CD163, and heme-oxygenase 1 were measured. To evaluate oxidative and inflammatory pattern, these investigators also quantitated myeloperoxidase, IL-10, and VCAM1. Consistent with earlier findings, it was reported that plaques with Hp2-2 allele had increased hemorrhage, increased heme-oxygenase, decreased CD163 protein, increased MPO, and decreased IL-10. Some of these unfavorable changes appear to be associated with oxidative stress, since patients with Hp2-2 genotype had greater oxidative stress [245]. Thus, these independent studies demonstrated that haptoglobin, an HDL-associated proinflammatory protein and a risk factor for CVD, is elevated in diabetes; especially the Hp2-2 allele show stronger correlation with CVD risk factors.

Conclusion

As a working hypothesis, the biologic sequence of events that leads to HDL dysfunction is shown in Fig. 5. HDL performs its normal function by removing cholesterol from lipid-laden macrophages in the arterial wall, thus causing lesion regression. In high oxidative environment, the inflamed macrophages entrapped in the subendothelial space secrete proinflammatory cytokines and haptoglobin, and activates wnt signaling through LRP5/6 as a result of uptake of aggregated LDL [246] in hyperlipidemic conditions. Wnt/β-catanin signaling has been shown to induce proliferation of vascular smooth muscle cells [247], which may lead to narrowing of artery lumen and eventually causing occlusion. High oxidative stress, diabetes, and proinflammatory proteins, including acute phase proteins like haptoglobin and CRP cause dysfunctional HDL, leading to dampening of cholesterol efflux capability and impaired arterial cholesterol removal. Treatments that attenuates hyperlipidemia, oxidative stress and inflammation, at least in animal models of diabetes and hyperlipidemia, improves HDL function [248] and promotes removal of cholesterol from lipid-laden macrophages entrapped in the subendothelial space leading to atherosclerotic lesion regression [248]. Thus, systemic metabolic disturbances of diabetes, including hyperglycemia and hyperlipidemia, likely play a central role in the pathogenesis of diabetes-associated atherosclerosis through the generation of oxidative stress and inflammation, and aggressive treatment of diabetes mellitus offer promise to reduce progression of CVD in this highly susceptible group of individuals with diabetes.

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Compliance with ethical standards

Conflict of interest During the preparation of this manuscript, the Rai Ajit K. Srivastava served as a consultant to Gemphire Therapeutics and currently employed at Gemphire Therapeutics Inc. The author has no conflict of interest.

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