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HDL dysfunction in diabetes: causes and possible treatments

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Abstract

HDL is known to be inversely correlated with cardiovascular disease due to its diverse antiatherogenic functions. These functions include cholesterol efflux and reverse cholesterol transport, antioxidative and anti-inflammatory activities. However, HDL has been shown to undergo a loss of function in several pathophysiological states, as in the acute phase response, obesity and chronic inflammatory diseases. Some of these diseases were also shown to be associated with increased risk for cardiovascular disease. One such disease that is associated with HDL dysfunction and accelerated atherosclerosis is diabetes mellitus, a disease in which the HDL particle undergoes diverse structural modifications that result in significant changes in its function. This review will summarize the changes that occur in HDL in diabetes mellitus and how these changes lead to HDL dysfunction. Possible treatments for HDL dysfunction are also briefly described.

Keywords

diabetes mellitus; dyslipidemia; glycation; HDL; HDL; inflammation; oxidation dysfunction

Diabetes mellitus (DM) is a major public health issue. Vascular complications are among the most common sequelae of the condition, as cardiovascular disease (CVD) accounts for 65% of mortality in DM and end-stage renal disease develops in approximately a third of all DM patients. Diabetic CVD accounts for approximately 35% of CVD-related hospitalizations, and DM remains one of the major causes of blindness in the Western world [1].

Since the Framingham study, it has been established that a positive correlation exists between LDL cholesterol [2] and CVD and an inverse correlation exists between HDL cholesterol and CVD [3]. Initial research focused on lowering LDL cholesterol, while elucidating the antiatherogenic functions of HDL. These studies revealed that HDL participates in the cholesterol efflux from peripheral cells and reverse cholesterol transport from these cells to the liver. Following studies have shown that HDL also acts as an

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Financial & competing interests disclosure

AP Levy is the author of a patent owned by his university that claims the pharmacogenomic use of the haptoglobin genotype to predict susceptibility to diabetic cardiovascular disease and to select which individuals will derive benefit from antioxidant therapy. AP Levy is now serving as a consultant for Haptocure, which has licensed this patent from his institution. This work was supported by grants from the BSF and NIH (RO1DK085226) to AP Levy. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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antioxidant by neutralizing oxidized lipids, and as an anti-inflammatory particle by inhibiting various inflammatory responses [4].

As research progressed it became clear that the biological activity of HDL is highly variable, shifting from an antiatherogenic to a pro-atherogenic moiety in various pathophysiological states. The loss of HDL antiatherogenic activity was termed HDL dysfunction. Type 2 diabetes represents a state in which HDL becomes dysfunctional [5]. In this review, the causes of HDL dysfunction in diabetes will be discussed. Possible HDL-based therapies will also be briefly reviewed.

HDL subclasses

HDL is commonly divided into various subclasses, according to its density, size, electrophoretic mobility and apolipoprotein cargo. HDL is separated into two subclasses according to density, in which HDL₂ particles range between 1.063 and 1.125 g/ml and HDL₃ particles range between 1.125 and 1.21 g/ml. These fractions can be further divided by diameter to HDL_{2b}, HDL_{2a}, HDL_{3a}, HDL_{3b} and HDL_{3c} subclasses, with HDL_{2b} having the largest diameter and HDL_{3c} having the smallest diameter. HDL₂ and HDL₃ share electrophoretic mobility due to their highly negatively charged surface phospholipids and are termed α -HDL. This subclass is the major carrier of plasma Apo-AI. Pre- β -HDL, whose electrophoretic mobility differs from that of α -HDL, carries only 5% of Apo-AI. Interestingly, pre- β -HDL particle's density range is narrow, around 1.21 g/ml, but they are extremely diverse in diameter, ranging from small 5.4-nm pre- β_1 particles to 14-nm pre- β_2 particles. Last, the presence of Apo-AII also defines Apo-AI-containing HDL particles, where Lp-AI is devoid of, and Lp-AI and Lp-AII carry Apo-AII [6,7].

HDL function

Reverse cholesterol transport & cholesterol efflux

One of the more recognized roles of HDL is the extraction of cholesterol from vascular beds and transporting it to the liver and steroidogenic organs, either directly or through other lipoproteins. It also best describes physiological HDL metabolism.

HDL is formed from lipid-free Apo-AI, which is synthesized *de novo* by the liver, or released from triglyceride-rich lipoproteins particles. Maturation of lipid-free Apo-AI to nascent or discoid HDL occurs via the binding of Apo-AI to ATP-binding cassette A1, a process that is necessary for phospholipid transfer. Cholesterol efflux from the cell membrane to HDL may occur, either following or in concert with the transfer of phospholipids, depending on the cellular receptor and HDL subclass, via passive diffusion or active transport. Passive cholesterol efflux occurs either by aqueous diffusion or through scavenger receptor class B Type 1 (SR-BI). While HDL₂ and HDL₃ accept cholesterol by aqueous diffusion to a similar extent, HDL₂ interaction with SR-BI leads to increased passive efflux compared with that achieved by the interaction of HDL₃ and SR-BI. In humans, active efflux occurs through ATP-binding cassette A1 and simultaneously with the transfer of phospholipids to lipid-free Apo-AI. Other determinants of efflux through the passive and active pathways are phospholipid saturation, which accelerates the active pathway and decelerates the passive pathway, and the amount of cholesterol in the cells, which significantly increases active trafficking with only a mild effect on passive trafficking [7].

Cholesterol that reaches HDL particles is converted to cholesteryl esters by the HDL-associated enzyme lecithin-cholesterol acyltransferase (LCAT). Cholesteryl esters are more hydrophobic than cholesterol, and thus they move into the lipid core. This process

supposedly prevents retrograde cholesterol diffusion back into cells and allows a more continuous and efficient efflux [8]; however, studies demonstrating LCAT deficiency is not associated with decreased cholesterol efflux suggest that this process is not imperative for normal HDL function [7]. Still debated is the question of whether LCAT deficiency accelerates the progression of CVD, as some studies found no such association [9,10], while others did [11].

Further remodeling of the HDL particle is performed by CETP, PLTP and hepatic lipase (HL). CETP mediates the exchange of cholesteryl esters for triglycerides between the various lipoproteins [8]. In HDL, CETP action depletes the particle from cholesteryl esters and enriches it with triglycerides, which are hydrolyzed by HL to form small dense HDL particles. PLTP participates in several steps of HDL modification. First, it transfers phospholipids from VLDL and intermediate-density lipoprotein to HDL. This process is also important for the preservation of the pool of free phospholipid-rich surface fragments, which are necessary for the production of new HDL particles in the plasma. Second, PLTP catalyzes the fusion of small HDL particles (HDL₃), during which process larger HDL particles (HDL₂) are formed and lipid-poor or -free Apo-AI is released [12]. Lipids are also transferred directly from HDL to the liver via the SR-BI and CD36, in a process named cholesterol influx [13]. Similar to cholesterol efflux, cholesterol influx is dependent on HDL size, whereby large HDL particles are better donors than small HDL particles [7]. This process is largely modulated by Apo-AII, which decreases binding of HDL to scavenger receptors and cholesterol influx [13].

Catabolism and elimination of HDL particles, as opposed to HDL lipids, is a process that is poorly understood. Small HDL particles, of a diameter of less than 8 nm, are filtered in the glomeruli to the urine, and then taken up by the receptors cubulin and megalin in the proximal tubule to be degraded in lysosomes [8]. The identity of the HDL proteins that mediate binding to megalin are debated, as some claim that these are only Apo-AI and Apo-AIV [14], while others present evidence for Apo-AII binding as well [15]. Hepatic degradation has also been suggested [8], although the receptors mediating this elimination pathway remain elusive.

Antioxidative function of HDL

The ability to attenuate the process of LDL oxidation is another major antiatherogenic function of HDL. The antioxidant activity of HDL is achieved by both protein and lipid moieties.

Apo-AI, which has a major role in cholesterol efflux, is also a pivotal antioxidant protein. The methionine residues of Apo-AI reduce lipid peroxides (LOOH) to nonreactive lipid hydroxides (LOH), thus terminating the redox chain. Moreover, free Apo-AI removes seeding molecules, such as hydroperoxyeicosatetraenoic acid and hydroperoxyoctadecadienoic acid [16]. Other HDL apo-lipoproteins, such as Apo-E and Apo-J, may also possess such antioxidant activity [17]. LCAT, paraoxonase-1 (PON1) and platelet-activating factor acetylhydrolase also possess antioxidant capacities, but their interaction is with short-chain oxidized phospholipids rather than with lipid peroxides [18]. Lipid-soluble components of HDL, such as vitamin E, also contribute to its antioxidant function, as they act as reducing agents of lipid peroxides [19].

Recently, a novel and exciting role for HDL, and specifically, Apo-AI, has been identified. Lipid-free Apo-AI and reconstituted HDL were both shown to inhibit glucose-induced oxidative stress in macrophages by inhibiting Nox2 protein expression on one hand, while increasing superoxide dismutase expression on the other. These effects are mediated by the same cellular receptors that induce cholesterol efflux: ABCA-1 and SR-BI, thus forming

another connection between HDL antioxidative activity and reverse cholesterol transport activity [20].

Anti-inflammatory function of HDL

The concept that HDL has anti-inflammatory capacities is novel and is still evolving. Initial studies focused on the link between the anti-inflammatory properties of HDL that arise from its antioxidative ability. In these studies, HDL was shown to inhibit oxidized LDL-induced MCP-1 production and monocyte transmigration in a coculture of human aortic endothelial cells and human aortic smooth muscle cells [21,22]. This was developed into a functional assay termed 'HDL inflammatory index', which measures the ability of HDL to prevent or enhance LDL-associated chemotactic activity.

More recent studies have focused on the anti-inflammatory properties of HDL, which are independent of its antioxidative functions. HDL was demonstrated to blunt the inflammatory response of endothelial cells to stimuli such as TNF- α and IL-1, as shown by the decrease in VCAM-1 [23], ICAM-1 and E-selectin [24]. HDL and lipid-free Apo-AI were shown to inhibit T cell-mediated macrophage secretion of proinflammatory cytokines and chemokines [25] by directly binding to T cells [26] and to T cell-derived microparticles [27], thus preventing the interaction between the activated T-cell receptor and the macrophage. Using a microarray assay, Suzuki *et al.* have demonstrated that inflammatory factors regulated by the TRAM/TRIF pathway are the primary target for HDL inhibition following a lipopolysaccharide challenge of macrophages [28].

HDL levels, structure & function in diabetes

Diabetes is associated with quantitative changes in the amount of circulating lipids – notably an increase in triglycerides, elevated LDL and a reduction in HDL. Like other lipoproteins, HDL also undergoes significant qualitative changes in diabetes, in both structure and function. However, since dyslipidemia may be present several years before the onset of diabetes, it is hard to determine which of these changes are related to the pathognomonic features of the disease, and which precede and accelerate its progression [29]. In fact, the role of cholesterol metabolism and HDL function in the pathogenesis of Type 2 diabetes mellitus (T2DM) has recently gained a lot of attention. Native Americans carrying the R230C mutation in ABCA-1, which is associated with decreased cholesterol efflux capacities, were shown to be more prone to early age T2DM. Mice studies suggest that cholesterol accumulation in islet β -cells is the reason for their pathology. HDL also appears to protect β -cells from the toxic effects of glucose and IL-1 β , and to enhance insulin secretion. In skeletal muscles, HDL was demonstrated to increase insulin activity in the form of glucose uptake. This activity was dependent on ABCA-1 activity, and included activation of AMP kinase [30].

Recent studies have shown that many factors contribute to the HDL dysfunction that is witnessed in T2DM. Oxidation and glycation of HDL-associated proteins were shown to render them inactive. By changing the gene expression and activity of HDL-metabolizing enzymes, metabolic abnormalities associated with DM compromise the efficiency of reverse cholesterol transport. Finally, the constantly increased inflammatory state results in major changes in the HDL proteome; changes that not only devoid the HDL of its normal function, but also turn it into a proatherogenic particle.

Diabetic dyslipidemia: changes in HDL metabolism

Dyslipidemia is a key feature of T2DM, and may precede it by several years. Diabetic dyslipidemia is characterized not only by a change in the levels of lipoproteins and the ratio

between them, but also by changes in the structure of the lipoproteins themselves. The increase in VLDL and triglycerides presents as an increase in VLDL1 production. Small dense LDL particles are detected to a much larger extent in T2DM, although LDL levels remain grossly unchanged. HDL levels were found to be decreased in T2DM, with a predominance of small dense HDL particles that undergo rapid catabolism [29,31]. This alteration in HDL is the result of an augmentation in the activity of several lipolytic and HDL-modifying enzymes, alongside an increment in triglyceride levels.

In T2DM, hypertriglyceridemia results from insulin resistance, hyperglycemia and hyperinsulinemia – accelerated lipolysis following insulin resistance increases the availability of free fatty acids, while hyperglycemia and hyperinsulinemia trigger triglyceride synthesis in the liver through the activation of ChREBP [32] and SREBP1c [33], respectively. As a result, the mass and activity of CETP also increases [12]. In these conditions, the action of CETP leads to the enrichment of HDL particles with triglycerides, while depleting them from cholesteryl esters, thus decreasing HDL cholesterol levels [18]. HL, which is upregulated by hyperglycemia [34] and has increased activity in states of insulin resistance [35,36], rapidly metabolizes the triglyceride-rich HDL, forming small HDL particles that undergo accelerated clearance, as mentioned above. Moreover, HL enhances the depletion of HDL cholesteryl esters [37]. The changes in the HDL lipid composition also destabilize Apo-AI, leading to its shedding from HDL during lipolysis [38]. Finally, the mass of lipoprotein lipase that is responsible for the lipolysis of triglyceride-rich lipoproteins, a process in which HDL precursors are released, is decreased in T2DM, thus reducing the material necessary for the assembly of new HDL particles [37].

Effects of hyperglycemia & glycation on HDL structure & function

Glycation of HDL and Apo-AI, a process that is known to occur in diabetes *in vivo* [39], is known to have a negative effect on the activity of HDL-associated antiatherogenic enzymes. *In vitro* studies have demonstrated that the process of HDL glycation was shown to be accompanied by the oxidation of HDL lipids [40,41]. *In vitro* glycation of HDL was shown to decrease cholesterol efflux [42] and attachment of HDL to fibroblasts [43], although some studies did not observe such effects [44,45]. Hyperglycemia and formation of advanced glycation end products impair cholesterol efflux, not only by interacting with HDL, but also by interacting with cholesterol-donating cells, where they decrease the expression of ABCA-1 [46] and SR-BI [47].

Hyperglycemia and glycation may also contribute to HDL dysfunction by decreasing its antioxidative capacity. Glycation was shown to significantly decrease PON1 *in vitro* [40,41,48], and *in vivo* PON1 activity was found to be negatively correlated with levels of advanced glycation end-products [49]. Similarly, LCAT activity is negatively associated with HbA_{1c} levels, a marker of plasma protein glycation, in T2DM [50]. Glycation of Apo-AI was proposed as a mechanism for LCAT inactivation as it decreases the ability of Apo-AI to bind LCAT, a process that is imperative for the latter protein's function [51].

A recent study also demonstrated the deleterious effects of HDL glycation on its anti-inflammatory function, showing that glycated lipid-free Apo-AI infusion did not decrease adhesion molecule expression following vascular injury, as opposed to normal lipid-free Apo-AI [52]. Further research may elucidate the effect of HDL glycation on other inflammatory interactions, such as response to proinflammatory cytokines and T-cell chemotactic activity.

Effect of oxidation on HDL function

Similar to the effects of glycation, oxidative modifications of HDL were also shown to be associated with impairment in its function. Indeed, a series of studies by several groups has demonstrated a decrement in cholesterol efflux following various oxidative modifications of Apo-AI. Using mass spectrometry, Zheng *et al.* have shown that HDL oxidation, as measured by chlorination and nitration of tyrosine residues, negatively correlates with ABCA-1-dependent cholesterol efflux [53]. Heinecke *et al.* observed that HDL modified by products of the myeloperoxidase system is increased in atherosclerotic lesions and in the plasma of coronary artery disease patients [54], and that some of these modifications, namely chlorination, impair ABCA-1-specific cholesterol efflux [55–57]. Two amino acids that were found to be targets for oxidative modifications on Apo-AI, Tyr-166 and Met-148, were localized to the binding site of LCAT. Oxidative modifications of these amino acids were shown to inhibit the binding of LCAT to Apo-AI and, thus, abolish its activity [58,59].

The link between HDL oxidation and function has also been exemplified by the effect of the haptoglobin (Hp) genotype on HDL function and the response to vitamin E treatment in the setting of DM. Hp is the primary carrier of extracorporeal hemoglobin (Hb) in the plasma. Once released from erythrocytes, Hb catalyzes the production of reactive oxygen species (ROS) via Fenton chemistry, damaging its surrounding tissues and plasma moieties. This process is attenuated, but not abolished, upon Hp binding to Hb, an event that is likely to occur owing to the high levels of Hp in the serum and the high affinity of Hp to Hb. The Hb–Hp complex is cleared from the bloodstream and tissues by the CD163 receptor, which is expressed by macrophages and liver Kupffer cells. The antioxidant capacity of Hp is heavily dependent on the Hp genotype, as *Hp2-2* is inferior to *Hp1-1* in its ability to prevent ROS formation by Hb [60], although their affinity is similar. Clearance rate by the CD163 receptor also differs between the Hp genotypes, as the Hp 1-1–Hb complex is cleared more rapidly than the Hp 2-2–Hb complex [61]. These differences are magnified in the settings of DM: glycosylation and oxidative modifications of Hb increase differences in ROS production between the Hp types, and peripheral blood monocytes and atherosclerotic plaque macrophages of *Hp 2-2* DM individuals express lower levels of the CD163 receptor, allowing a prolonged presence of the complex within the tissues and bloodstream [60,62].

Lipoproteins are among the blood-born moieties that can be harmed by free Hb. Hb was shown to oxidize LDL, both in a mechanism dependent on H₂O₂ oxidation of heme and formation of Fe^{IV} [63], and a mechanism independent of H₂O₂ in which heme is transferred from methemoglobin to LDL [64]. Hp was shown to mitigate the latter process, with Hp 1-1 having a stronger inhibitory effect on heme transfer compared with Hp 2-2 [65]. Hb binding to HDL appeared to be increased in dietary and genetic atherosclerosis mice models, and in coronary artery disease patients, resulting in greater NO consumption and impaired arterial vasoactivity [66]. For HDL, the formation of a complex of Hb with Hp appears to cause oxidative stress, rather than inhibit it. Hp interacts with HDL through two of its major proteins, Apo-AI [67] and Apo-E [68]. Thus, Hp adjoins Hb and HDL in a manner that would exist to a lesser degree in its absence. In coronary heart disease patients, Hp- and Hb-associated HDL levels were shown to be correlated with an increased HDL inflammatory index and HDL oxidation [69]. Quantitatively, there is more Hb bound to HDL in the serum of *Hp 2-2* DM individuals compared with *Hp 1-1* DM individuals, resulting not only from the attenuated clearance of the Hp–Hb complex in *Hp 2-2* DM, but also from the size of the Hp molecule itself – while in the *Hp1-1* genotype Hp dimers are found, in the *Hp2-2* genotype the protein is in a multimeric cyclic form of three to six Hp monomers. Thus, the HDL in *Hp 2-2* DM individuals is more oxidized, as demonstrated by the increased levels of lipid peroxides, compared with *Hp 1-1* DM individuals [70]. This translates to significant changes in HDL function, as cholesterol efflux, reverse cholesterol transport and cholesterol

esterification are decreased in the setting of *Hp 2-2 DM* individuals compared with *Hp 1-1* [71]. Moreover, proving that HDL-associated oxidative stress is the reason for HDL dysfunction, vitamin E supplementation successfully decreased HDL-associated lipids and increased cholesterol efflux in *Hp 2-2 DM* individuals [70].

Another HDL protein that appears to be sensitive to oxidation is PON1, which undergoes inactivation following HDL oxidation [72], or exposure to oxidized LDL [73] and linoleic acid hydroperoxide. PON1 inactivation by linoleic acid hydroperoxide appeared to involve the latter's reduction to a hydroxide, and was reversible following treatment with cysteine [74].

Inflammation

It is well recognized that a chronic inflammatory state is a feature of DM. Inflammation was discovered to be a major determinant of HDL function due to the changes in the HDL proteome. During an acute phase response, the HDL proteome dramatically changes, converting it from an antiatherogenic particle to a raft of immunological proteins. The Apo-AI content was found to be dramatically decreased during an acute phase response and replaced mostly by the acute phase protein, serum amyloid A [21]. Other HDL-associated proteins that are decreased during an acute phase response are LCAT and PON-1 [75].

These changes were found to decrease both the ability of HDL to induce cholesterol efflux from macrophages and reverse cholesterol transport from peripheral tissues to the liver [76–78]. The activity of HDL antioxidant enzymes, PON1, PAF-AH and LCAT, is also decreased during an acute phase response [21]. Inflammation also turns the HDL into a proinflammatory particle, raising the HDL inflammatory index to values above one [79], meaning HDL increases the inflammatory response elicited by oxidized LDL rather than mitigates it.

A novel and interesting effect of the proteome change that HDL undergoes during inflammation is its ability to bind components of the extracellular matrix. The enrichment of HDL with serum amyloid A facilitates binding to proteoglycans, retaining it in the vascular bed and eventually increasing its oxidation [80]. Mass spectrometry studies of HDL from coronary disease patients revealed that it is enriched with another inflammatory protein, complement component 3 (C3) [81,82]. The specific biological consequence of C3 binding to HDL is still unknown, but it has been observed that C3 levels are increased in the atherosclerotic plaque [83], and that increased plasma levels of C3 are correlated with myocardial infarction [84].

Expert commentary & five-year view

Treatment of HDL dyslipidemia

HDL dyslipidemia may be treated in several ways. Certainly the most common approach to date has been to try to raise HDL levels with the notion that 'more is better'. However, as we have reviewed here, particularly in the setting of DM this may not be the case. The concept of targeting HDL quality rather than quantity has only recently become appreciated. Several treatment options are under study targeting HDL metabolism, HDL oxidation and even providing HDL mimetics.

One of the first treatments that was aimed at interfering with HDL metabolism, and therefore, increasing HDL levels, was the CETP inhibitor torcetrapib. Indeed, initial studies have shown that torcetrapib raises HDL cholesterol in humans [85,86]. However, clinical studies have shown that it does not decelerate the progression of atherosclerosis [87,88] and it has been associated with increased morbidity and mortality [89], perhaps due to its

hypertensive effects [90]. Recent studies propose that the adverse effects of torcetrapib are not related to the inhibition of CETP. A wide genetic study has shown that SNPs in the *CETP* gene that decrease its activity do not produce hypertensive effects such as those seen with torcetrapib treatment [91]. Torcetrapib, as opposed to the novel CETP inhibitor, dalcetrapib, whose structure is dissimilar to that of torcetrapib, was shown to upregulate the expression of L-type calcium channels, providing a plausible mechanism independent of CETP inhibition to the elevation in blood pressure following torcetrapib treatment [92]. Indeed, initial studies with CETP inhibitors other than torcetrapib prove them to be safe in terms of hypertensive effects [93].

Niacin treatment, which raises HDL cholesterol by increasing cholesterol efflux and inhibiting triglyceride release from adipose tissue, was shown to be beneficial in a randomized placebo-controlled clinical trial [94]. However, intolerance and adverse effects in the form of compromised glycemic control has decreased its applicability and limited its use [95]. The ability of Niaspan, a high-dose modified-release form of niacin, whose adverse effects are mitigated, to induce similar clinical effects is currently being examined and was already shown to attenuate the progression of carotid atherosclerosis in a group of simvastatin-treated patients [96].

Another exciting potential therapy for dysfunctional HDL is the administration of Apo-AI mimetic peptides or of Apo-AI Milano. Apo-AI mimetic peptides are not homologous to Apo-AI, but their tertiary structure, namely a class A amphipathic helix, is similar to that of the Apo-AI protein. Apo-AI mimetic peptides were shown to possess antioxidative and anti-inflammatory capabilities in both *in vitro* and *in vivo* models [97]. They were also shown to attenuate atherosclerosis progression in diabetic *Apo-E*^{-/-} mice [98]. Recently, Apo-AI mimetics were demonstrated to enhance HDL function and decrease HDL oxidation in T2DM patients [99]. However, in a recent clinical trial, the administration of Apo-AI mimetic peptides did not improve HDL anti-inflammatory or antioxidant function [100]. Apo-AI Milano is a naturally occurring mutated form of Apo-AI in which the cysteine residue 173 is switched to arginine. People carrying Apo-AI Milano were shown to have extremely low HDL levels (<30 mg/dl), but low rates of atherosclerosis. Infusion of Apo-AI Milano complexed with phospholipids was shown to cause regression of coronary atherosclerosis in humans [101]. Moreover, Apo-AI Milano was found to stabilize the atherosclerotic plaque to a greater extent than native HDL in a mouse model, owing to increased anti-inflammatory activity [102].

Although discredited over the last few years, antioxidant therapy may also prove useful when given to the appropriate population of patients. Vitamin E supplementation to T2DM patients with the *Hp* 2-2 genotype has led to a significant decrease in HDL oxidative modification and a significant improvement in HDL function, while possibly harming patients of the *Hp* 2-1 genotype, in whom oxidative burden is decreased [103]. The beneficial effects of vitamin E supplementation to *Hp* 2-2 DM individuals were shown to translate into increased survival in a major clinical trial [104].

Our knowledge on the roles of HDL is constantly growing. First described as a mediator of reverse cholesterol transport, HDL is now known to have various antiatherogenic roles, including acting as an antioxidant and anti-inflammatory moiety. These abilities are compromised in several pathophysiological states, ultimately transforming HDL from an antiatherogenic to a proatherogenic particle.

Following the understanding that increased HDL levels may not always translate to increased HDL function, novel treatment strategies today focus not only on elevating HDL levels, but also on enhancing its function, as measured by anti-inflammatory, antioxidative

and cholesterol efflux activities. These treatments include prevention of HDL modification, as in the case of vitamin E; HDL replacement, as in the case of Apo-AI mimetics; and elevation of HDL, as in the case of Niaspan and CETP inhibitors.

While much is known regarding the antiatherogenic roles of HDL, its role as an integral part of the innate immune system is largely obscure. Research in this field may allow the use of HDL-directed therapies, not only for the prevention of CVD, but also for the treatment of infectious diseases.

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Key issues

- HDL possesses various antiatherogenic properties, including reverse cholesterol transport, antioxidative and anti-inflammatory capacities.
- The antiatherogenic properties of HDL are compromised in diabetes mellitus (DM), due to oxidative modification and glycation of the HDL protein and transformation of the HDL proteome to a proinflammatory profile.
- Metabolic abnormalities in DM significantly change the lipid composition of HDL, resulting in its rapid catabolism.
- Treatments today should not only focus on increasing HDL cholesterol, but also on improving its function.
- Understanding the pathological mechanisms underlying HDL dysfunction may allow the allocation of unique therapies for specific populations, as with *Hp 2-2* DM individuals and vitamin E supplementation.
- Further research is needed to elucidate the role of the inflammatory HDL particle.