High-Density Lipoprotein Alterations in T2D and Obesity

Subjects: Endocrinology & Metabolism

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Alterations affecting high-density lipoproteins (HDLs) are one of the various abnormalities observed in dyslipidemia in type 2 diabetes mellitus (T2DM) and obesity. Kinetic studies have demonstrated that the catabolism of HDL particles is accelerated. Both the size and the lipidome and proteome of HDL particles are significantly modified, which likely contributes to some of the functional defects of HDLs. Studies on cholesterol efflux capacity have yielded heterogeneous results, ranging from a defect to an improvement. HDLs are less able to inhibit the nuclear factor kappa-B (NF-κB) proinflammatory pathway, and subsequently, the adhesion of monocytes on endothelium and their recruitment into the subendothelial space. In addition, the antioxidative function of HDL particles is diminished, thus facilitating the deleterious effects of oxidized low-density lipoproteins on vasculature. Lastly, the HDL-induced activation of endothelial nitric oxide synthase is less effective in T2DM and metabolic syndrome, contributing to several HDL functional defects, such as an impaired capacity to promote vasodilatation and endothelium repair, and difficulty counteracting the production of reactive oxygen species and inflammation

high-density lipoprotein type 2 diabetes obesity metabolic syndrome

1. HDL Size and Composition

High-density lipoproteins (HDLs) are composed of apolipoproteins (mainly apoA-I), non-structural proteins, and lipids. They are a heterogeneous group of particles that vary in size as well as protein and lipid composition. Basically, HDLs are composed of a surface monolayer, made up of amphipathic phospholipids (PLs) and sphingolipids (SPLs) and unesterified cholesterol (UC) molecules, which surround the particle core, which consists of a mixture of hydrophobic TG and cholesteryl ester (CE) molecules. The alterations in HDL size and composition in contexts of insulin resistance are important because there is a close relationship between HDL size and composition and their functions. An overview of the changes in HDL size and composition is presented in **Figure 1**.

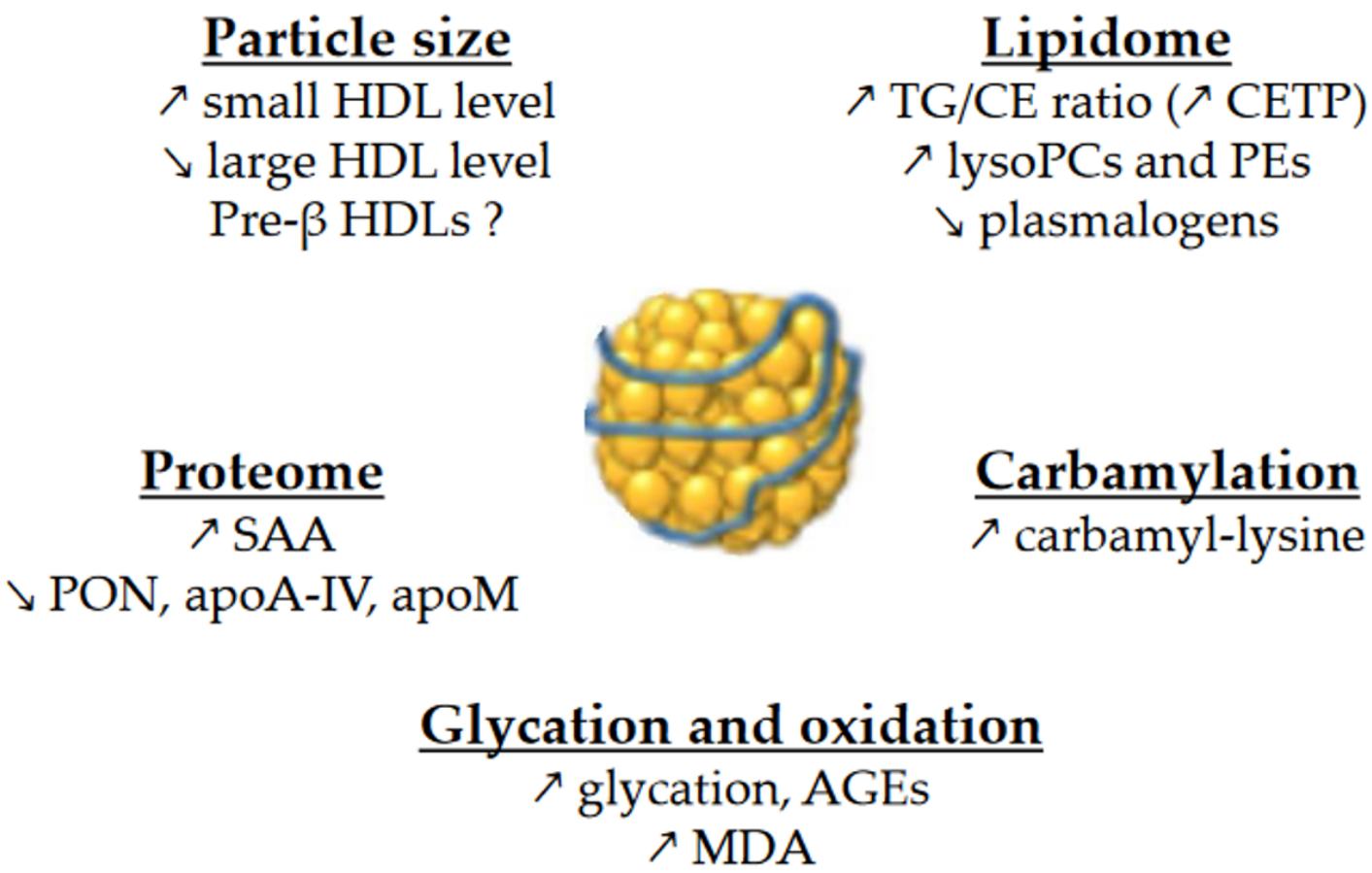

Figure 1. Main changes in the size and composition of HDLs in T2DM and MetS. ↗ and ↘ mean increase and decrease, respectively. AGEs, advanced glycation end-products; CE, cholesteryl esters; CETP, cholesteryl ester transfer protein; MDA, malondialdehyde; PCs, phosphatidylcholines; PEs, phosphatidylethanolamines; PON, paraoxonase; SAA, serum amyloid A; TG, triglycerides.

1.1. Particle Size

Size-based HDL nomenclature can be confusing because it depends on the technology used to separate HDL subclasses. In any case, HDLs are classified as very small, small, medium, large and very large particles. Classically, those particles are called HDL2a and HDL2b (large), HDL3a, HDL3b, and HDL3c (medium or small) and unlipidated apoA-I or pre-β (discoidal).

Overall, the size of HDLs is decreased in T2DM [1][2]. More precisely, nuclear magnetic resonance spectroscopy studies revealed that small HDL particles are more numerous in T2DM, contrary to large HDL particles [3][4][5][6]. It is also the case in insulin-resistant individuals without diabetes [6][7][8], and the intensity of changes actually increases with the degree of insulin resistance [6].

1.2. Lipidome

HDL particles are enriched in TGs in patients with T2DM [1][2][9][10][11], obesity [12], insulin resistance [10][13] or MetS [14]. The replacement of CE by TG molecules in HDLs affects the conformation of apoA-I [15], which could modulate

binding to receptors and the functions of HDLs.

PLs and SPLs represent more than one third of the total mass of HDLs. They play a major role in HDL functions, either by binding to a specific receptor, such as sphingosine-1-phosphate (S1P) receptors or by modulating the physicochemical properties of HDLs. Lipidomic studies have revealed several changes in the HDL phosphosphingolipidome, although the results are quite heterogeneous. The expression of results in relation to either total HDL mass, total HDL lipids, or apoA-I levels makes it challenging to compare between studies. The HDL content in total PLs has been found to be either decreased in T2DM when the results are expressed in relation to total lipids [10], or normal when the results are expressed in relation to total mass or total lipids [1][11].

Taken together, phosphatidylcholines (PCs, the main PL class) and sphingomyelins (SMs) represent more than 80% of PLs/SPLs in HDLs. When the results are expressed in relation to apoA-I, the HDL content in PCs and SMs in T2DM has been found to be either normal or decreased [2][11]. When the results are expressed in relation to total HDL lipids, PCs and SMs have been found decreased in T2DM HDLs [10].

1.3. Proteome

Proteins form a major structural and functional component of HDL particles. The protein cargo of HDLs is comprised of over 100 proteins [16]. It should be noted that the HDL isolation method has a significant impact on HDL protein composition [17]. The HDL proteome has been extensively studied in diabetes, especially using mass spectrometry. Besides apoA-I, the kinetics of several HDL-proteins is perturbed in T2DM, as described hereafter. Reduced half-lives are observed for apoA-II, apoJ, apoA-IV, transthyretin, vitamin-D binding protein, and complement C3 [16]. A recent large proteomic study evaluated 182 proteins in isolated HDL fraction and found that HDLs from T2DM patients are enriched in 17 proteins and are deprived of 44 proteins compared to healthy individuals [5]. More precisely, HDLs were particularly enriched in pulmonary surfactant protein B and in serum amyloid A proteins (SAA1 and SAA2). In contrast, T2DM HDLs were deprived in apoA-IV, clusterin, paraoxonases (PON1 and PON3), apoD, apoE, apoF, apoM, apoC-II, and apoC-III [5]. The enrichment of HDLs in SAA in diabetes [5][18][19] is of particular interest due to its deleterious role in reverse cholesterol transport (RCT) [19][20].

1.4. Glycation and Oxidation

Chronic hyperglycemia in diabetes facilitates accelerated glycation, which is usually divided into early and late glycation. Thus, reducing sugar reacts with amino groups of proteins to form Schiff bases and then Amadori compounds (early glycation products). It may be followed by irreversible dehydration, condensation, and cross-linking reactions, resulting in a heterogeneous family of derivatives called advanced glycation end-products (AGEs), also known as late glycation products or glycoxidation products. Besides glucose itself, chronic hyperglycemia and oxidative stress in diabetes induces the production of dicarbonyls (glyoxal, methylglyoxal, 3-deoxyglucosone), which also react with proteins to yield AGEs [21]. Carboxymethyl-lysine (CML) is thought to be the most abundant AGE in vivo. Among the amino acids with nucleophilic residues prone to glycation, lysine residues are particularly abundant in apolipoproteins, and they are the preferred site of glycation.

The level of HDL glycation is significantly increased in T2DM, and seven glycation sites on lysine residues of apoA-I have been identified in T2DM subjects [22]. T2DM HDLs are enriched in methylglyoxal [23].

Beyond its role in the glycoxidation of HDL proteins, oxidative stress also leads to the peroxidation of lipids in HDLs. The proinflammatory enzyme myeloperoxidase (MPO) represents a major source of reactive-oxygen species (ROS) in atherosclerotic lesions. MPO-derived oxidants modify lipids and lead to the formation of dicarbonyls, such as malondialdehyde (MDA). The increased oxidative stress in subjects with T2DM and/or obesity is a consequence of several abnormalities, including hyperglycemia, insulin resistance, inflammation, and dyslipidemia [24]. Thus, not surprisingly, T2DM patients have increased concentrations of oxidized HDLs [25] and apoA-I [26], and their HDLs are enriched in MDA [27] and oxidized fatty acids derived from arachidonic and linoleic acids [28].

1.5. Carbamylation

Carbamylation (carbamoylation stricto sensu) is another post-translational modification affecting lipoproteins in diabetes. It is an irreversible non-enzymatic process mediated by isocyanate, and it is characterized by the binding of a carbamoyl moiety (-$CONH_2$) to lysine, resulting in carbamyl-lysine. It originates from MPO within atherosclerotic lesions or from urea or smoking. Plasma MPO levels are increased in T2DM [29][30], and patients with T2DM exhibit higher levels of carbamylated HDLs even without renal impairment [31][32].

2. HDL/apoA-I Kinetics

Numerous in vivo kinetic studies demonstrate that low HDL-C levels in T2DM and obesity are due to an accelerated catabolism of HDL particles [13][14][33][34][35]. The fractional catabolic rate (FCR) of HDL-apoA-I is increased, resulting in shorter plasma residence times for HDL particles [9][33][36]. Obese patients at an early stage of insulin resistance (i.e., without impaired glucose tolerance) already have an accelerated HDL-apoA-I catabolism [37].

Studies have found the production rate (PR) of HDL-apoA-I to be either elevated [9][13][34][36] or normal [14][37] in insulin-resistant individuals. The PR of HDL-cholesterol has recently been reported to be higher in patients with T2DM. In any case, the increase in HDL-apoA-I PR is usually smaller than the increase in the FCR, which explains the decreased concentrations of HDL-apoA-I. Interestingly, chronic endogenous hyperinsulinemia without insulin resistance (patients with insulinoma) does not induce an increase in the HDL-apoA-I PR [13]. This suggests that hyperinsulinemia per se is not responsible for the increased PR of HDL-apoA-I that is sometimes reported in patients with insulin resistance.

Glycation and glycoxidation may play a role in the accelerated catabolism of HDLs, although there is reportedly no correlation between HDL-apoA-I FCR and HbA_{1c} [35]. Thus, the turnover of glycated apoA-I is almost three times faster than its non-glycated counterpart [36]. In addition, the methylglyoxal modification of HDLs reduces plasma half-life in vivo [23]. Yet considerable evidence suggests that the kinetic properties of HDLs are linked to TG

metabolism. For instance, the HDL-apoA-I FCR in obese individuals is associated with triglyceridemia [38][39], VLDL-apoB PR [38], $VLDL_1$-TG FCR and PR [39], and also with the HDL-TG/CE ratio [37]. In T2DM, the HDL-apoA-I FCR is also positively associated with plasma TG [35] and with the TG content in HDLs [14][35]. HDLs enriched in TGs are hydrolyzed by hepatic lipase, leading to lipid-poor HDLs. Such HDLs are thermodynamically unstable and exhibit structural modifications in apoA-I, which facilitates both its dissociation from HDL particles [40] and its renal glomerular filtration [41].

3. HDL Functions

3.1. Reverse Cholesterol Transport

The best-known function of HDLs is their major role in RCT, which enables the removal of cholesterol from lipid-laden macrophages and artery walls. To sum up, HDLs promote cholesterol efflux from macrophage foam cells in atherosclerotic plaques either specifically by interacting with the transporters ABCA1 and ABCG1, or by aqueous diffusion, through a process facilitated by the scavenger receptor B1 (SR-B1). ABCA1 mediates cholesterol efflux preferentially to lipid-poor apoA-I and small dense HDLs, whereas ABCG1 transports cholesterol to the more mature lipidated HDL particles. Free cholesterol is then esterified by LCAT, and this esterification is important for maintaining the dynamics of cholesterol efflux. Cholesterol is ultimately cleared by the liver, either directly by selective uptake through SR-B1 or by a more recently discovered pathway mediated by F1-ATPase and P2Y13 receptor, or indirectly after CETP-mediated transfer to apoB-containing lipoproteins, which are then internalized by the LDL receptor. In addition to this classical hepatobiliary pathway, cholesterol can be also eliminated by a transintestinal pathway called transintestinal cholesterol efflux (TICE) [42].

Cholesterol efflux is thus the first step in the atheroprotective RCT pathway, and the cholesterol efflux capacity (CEC) of HDL particles is a crucial determinant of cholesterol clearance from lipid-laden macrophages. Over the past few years, studies have demonstrated that the CEC of HDLs is more strongly and inversely associated with incident cardiovascular events than the circulating HDL-C level itself [43][44].

Some authors reported an increased CEC in patients with T2DM [45] and in diabetic patients with hypertriglyceridemia [46]. ABCA1-dependent efflux was also increased using apoB-depleted serum from T2DM patients with hypertriglyceridemia compared to T2DM patients without hypertriglyceridemia [47]. On the other hand, CEC in T2DM patients was unmodified using fibroblasts and whole plasma [46][48][49], human THP-1 macrophages, and apoB-depleted serum [11], or when using THP-1 cells and HDLs isolated by dextran sulfate precipitation [28]. Lastly, CEC was decreased in T2DM patients using adipocytes and LpA-I (i.e., HDL particles containing apoA-I but not apoA-II) [50], Fu5AH hepatoma cells and whole plasma/serum [19][51][52][53][54][55], mouse peritoneal macrophages and isolated HDL3 [56], murine RAW264.7 macrophages and apoB-depleted serum [36], and also THP-1 macrophages and isolated HDLs [1][57]. Similarly, it was recently reported that small HDL particles and apoB-depleted serum from patients with T2DM both have impaired ABCA1-dependent CEC using baby hamster kidney (BHK) cells [36][58]. However, medium and large HDL particles had a similar capacity to promote ABCA1-specific

CEC in T2DM patients compared to control individuals in the study [58]. Otherwise, all three sizes of HDL particles from T2DM subjects had similar ABCG1-dependent CEC compared to controls [58].

Changes in lipid composition may also affect HDL CEC. In particular, the replacement of CE by TG molecules in HDLs affects the conformation of apoA-I [15] and could therefore modulate binding to receptors. In addition, the literature suggests that the content of HDLs in total PLs [59][60] and in SMs [61] modulates CEC, but, as mentioned above, the changes in these parameters are very heterogeneous across studies. Cardner et al. recently reported that CEC of apoB-depleted serum is mainly driven by apoA-I level in diabetic individuals [5].

3.2. Anti-Inflammatory Properties

Both diabetes and obesity are associated with low-grade inflammation, which substantially contributes to endothelial dysfunction and atherosclerosis. As shown in **Figure 2**, HDL particles exert an anti-inflammatory function by downregulating the expression of molecules involved in the recruitment of immune cells into the subendothelial space. These molecules include chemokine CCL-2 [62], vascular cell adhesion molecule (VCAM)-1, intracellular adhesion molecule (ICAM)-1, and selectin-E [11]. In addition, HDLs inhibit the release of inflammatory cytokines, such as TNF-α and IL-1β. The HDL anti-inflammatory function seems of particular relevance for CV outcomes, since it predicts new cardiac events in patients with myocardial infarction, independently of HDL-C [63]. Moreover, an inverse association between the anti-inflammatory capacity of HDLs and incident CV events was recently observed in a study of individuals from the general population cohort, independently of both HDL-C and CEC [64].

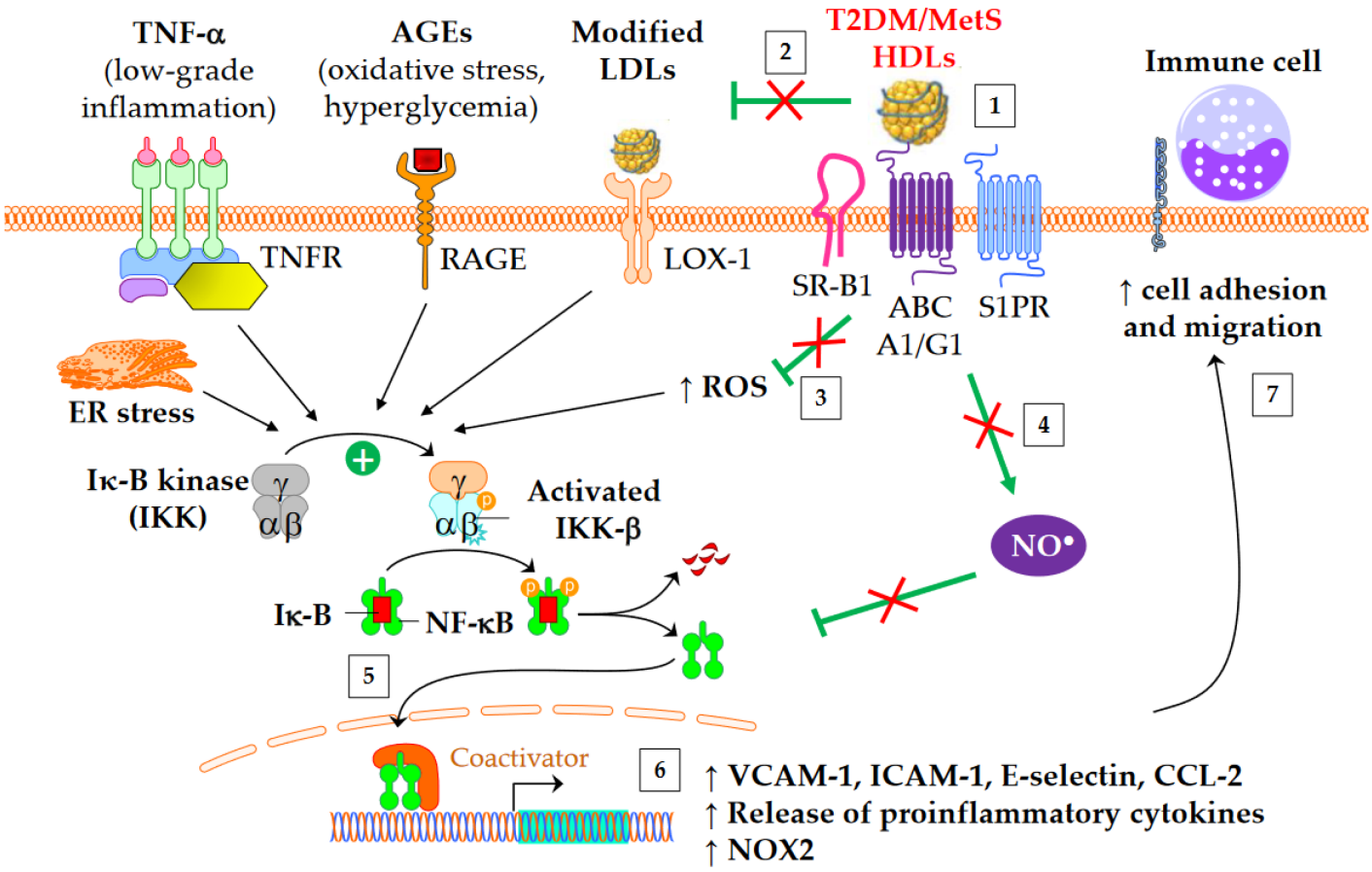

Figure 2. Anti-inflammatory functions of HDLs in T2DM and MetS. ↑ means increase. The inflammatory NF-κB pathway is triggered by several mediators, including TNF-α, advanced glycation end-products (AGEs), modified LDLs, reactive oxygen species (ROS), and endoplasmic reticulum (ER) stress. This leads to an increased gene expression of adhesion molecules, proinflammatory cytokines, and NADPH oxidase (NOX2). Green arrows represent the functions of healthy HDLs. (1) The binding of HDLs to receptors is modified by conformational changes in HDL particles in insulin resistant conditions. The depletion in S1P of MetS HDLs likely decreases the binding to S1P receptors (S1PR). (2) HDL-mediated protection of LDLs against oxidation is affected, (3) in particular due to the loss of capacity of HDLs to dampen ROS production. This promotes the NF-κB activation triggered by the recognition of oxidized LDLs by scavenger receptors in vasculature, particularly by LOX-1 (i.e., SR-E1) and SR-A1. (4) The activation of endothelial NO synthase by HDLs is reduced (see 4.3) and subsequently inhibits nitrosylation of NF-κB. (5) Ultimately, HDLs are less able to inhibit the translocation of NF-κB into the nucleus, and, (6) afterwards, the gene expression of adhesion molecules and proinflammatory cytokines. (7) This facilitates the recruitment of immune cells into the subendothelial space.

HDLs from T2DM patients are less able to inhibit the migration of monocytes towards endothelial cells [32][65]. Interestingly, this loss of function correlates with plasma SAA [65] and carbamylated HDL levels [32]. The fact that in vitro carbamylation of HDLs reproduces the loss of capacity to inhibit the migration of monocytes reinforces the potential role of carbamylated HDLs [32]. Although HbA_{1c} or glucose levels do not correlate with this loss of HDL function [65], some evidence suggests that glycoxidative changes in HDLs may play a role. Thus, the ex vivo

treatment of plasma with L-4F, an apoA-I mimetic peptide able to bind oxidized lipids with a higher affinity than apoA-I itself [66], restores the anti-inflammatory function of HDLs [65].

The activation of the classical IKK/IκB-α/NF-κB pathway plays a crucial role in the expression of adhesion molecules and in the release of proinflammatory cytokines into cardiovascular tissue. HDLs/apoA-I inhibit the NF-κB pathway via several overlapped mechanisms following interaction with SR-B1, S1PR, ABCA1, and ABCG1: cholesterol efflux, endothelial nitric oxide synthase (eNOS) activation [67] and subsequent S-nitrosylation [68], upregulation of 3β-hydroxysteroid-δ24 reductase [69][70] and heme oxygenase-1 [70], and inhibition of the toll-like receptors TLR4 [71] and TLR2 [72]. HDLs or apoA-I ultimately prevent NF-κB p65 subunit translocation to the nucleus and DNA binding [71], thus inhibiting the transcription of adhesion molecules, CCL-2, proinflammatory cytokines, and also NADPH-oxidase (NOX2) genes. It has been shown that HDLs isolated from T2DM patients are unable to suppress the activating phosphorylation of the NF-κB p65 subunit in endothelial cells [73]. Glycated apoA-I partially loses its ability to inhibit cytosolic IκB-α phosphorylation and NF-κB p65 subunit translocation to the nucleus [22].

3.3. Antioxidative Properties

T2DM and obesity are known to be associated with increased oxidative stress, which is closely linked to low-grade inflammation. In particular, oxidative stress in artery walls is responsible for the formation of oxidized LDLs (oxLDLs), rendering them more atherogenic. There are several mechanisms through which HDLs present in the intima can protect LDLs against oxidation [74]. HDLs directly protect LDLs from oxidation induced by one-electron oxidants (free radicals), and they are also able to remove oxidized lipids from LDLs. These activities can decrease local concentrations of oxLDLs. The antioxidative potential of HDL particles originates both from the activities of their proteins and from lipid components. Different HDL-associated apolipoproteins, lipid transfer proteins, and enzymes have been shown to contribute to the antioxidative capacity of HDLs.

3.4. Nitric Oxide Production

The production of nitric oxide (NO) is important for normal endothelial function and protects against endothelial dysfunction, an early hallmark of atherosclerosis. HDLs improve the bioavailability of NO in vasculature mainly by inducing the activating-phosphorylation of eNOS at serine 1177, which then promotes NO synthesis. NO production contributes to a number HDL's beneficial effects, such as vasorelaxation, inhibition of NF-κB pathway, and endothelium repair [75]. Several mechanisms are involved in eNOS activation mediated by HDLs. These include the binding of HDL-apoA-I to SR-B1 [76] and ABCG1 [77], the binding of HDL-S1P to S1PR1/3 receptors [78], the activation of mitogen-activated protein (MAP) kinases [79], the inhibition of protein kinase C (PKC) βII [67], cholesterol efflux facilitating the dissociation of eNOS from caveolin-1 [77], and, lastly, the suppression of ROS production which preserves from eNOS uncoupling.

An overview of NO-mediated HDL functions in T2DM and MetS is presented in **Figure 3**. HDLs from T2DM patients have been demonstrated to be less able to induce the activating-phosphorylation of eNOS at serine 1177

[73], NO production [27], and vessel relaxation [27]. Interestingly, eNOS phosphorylation and activity are even affected in obese patients in the absence of diabetes [80].

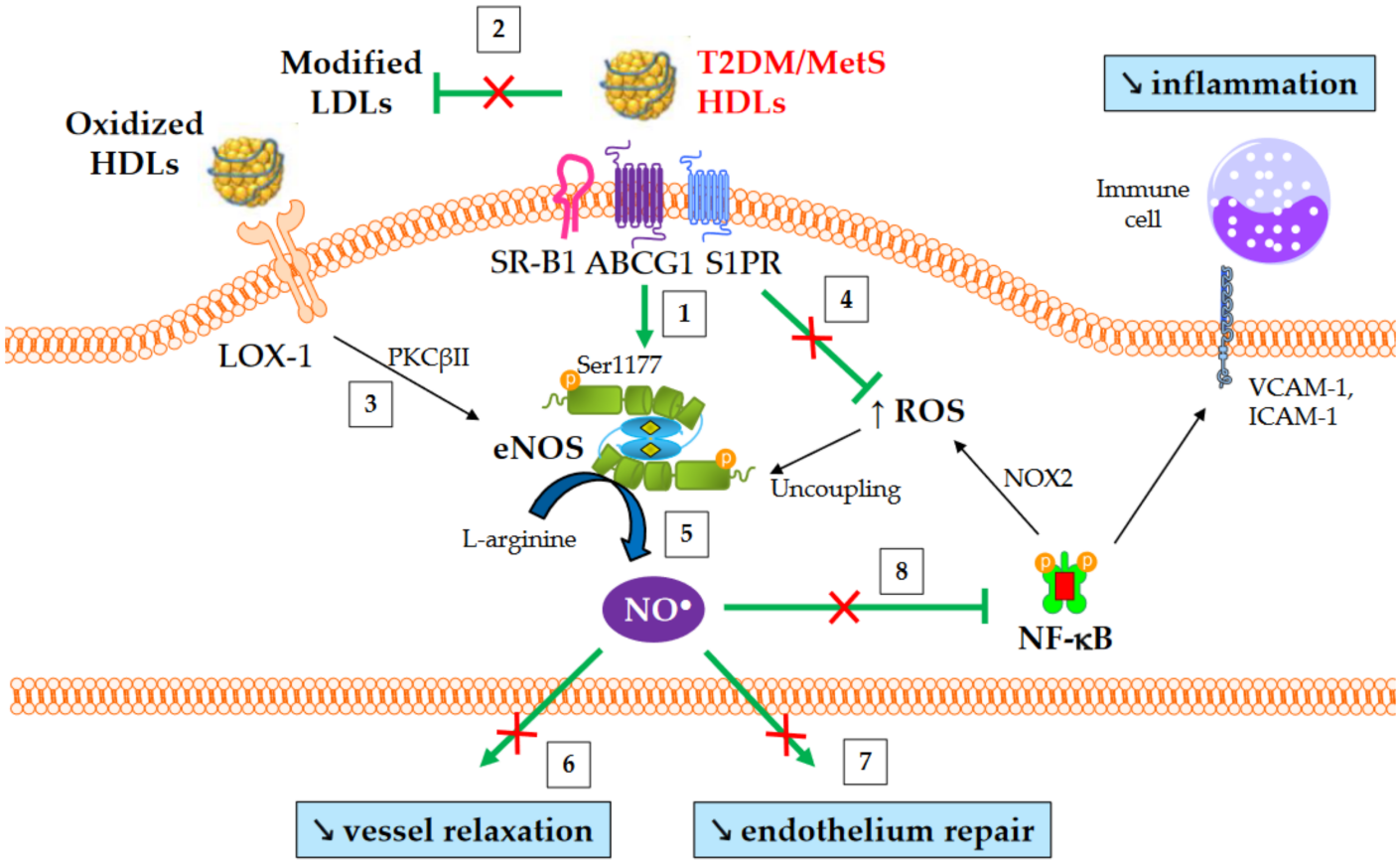

Figure 3. NO-mediated HDL functions in T2DM and MetS. ↑ and ↘ mean increase and decrease, respectively. Green arrows represent the functions of healthy HDLs. (1) HDLs from T2DM and non-diabetic MetS individuals are less able to induce Akt-dependent eNOS phosphorylation at Ser1177. (2) HDL-mediated protection of LDLs against oxidation is affected, thus facilitating eNOS inhibition after the binding of modified LDLs to LOX-1. (3) Oxidized HDLs are also able to bind to LOX-1 receptor, leading to PKCβII activation and subsequently to eNOS inhibition. (4) The loss of capacity of HDLs to dampen ROS production promotes eNOS uncoupling. (5) Ultimately, HDL-mediated NO production is reduced, (6) affecting the relaxation of vascular smooth muscle cells and (7) endothelium repair. (8) Reduced NO synthesis diminishes the inhibition of nitrosylation of NF-κB, as well as NOX2-mediated ROS production and the recruitment of immune cells into the subendothelial space.

3.5. Antiapoptotic Properties and Endothelium Repair

The integrity of endothelial cells is crucial for vascular homeostasis, and endothelial cell death triggers vascular damage and promotes inflammation and endothelial dysfunction. HDL particles can inhibit apoptosis in endothelial cells, thus preserving endothelium integrity [81][82][83].

The antiapoptotic activity of small HDL particles is reduced in MetS individuals [84][85], and is closely associated with altered physicochemical properties, such as core CE depletion and TG enrichment in apoA-I-poor HDL3c [84].

The depletion of HDLs in plasmalogens in T2DM and MetS may also play a role, since enrichment of rHDLs with plasmalogens enhances their antiapoptotic activity [81]. Changes in the HDL-apoM/S1P axis are also likely to be involved considering its important role in HDL antiapoptotic activity [82][86].

4. Antidiabetic Properties

Emerging data suggest that HDL particles could actually contribute to the development of diabetes. Firstly, HDL-C levels are inversely associated with T2DM development in epidemiological studies [87][88][89], and this metric has been included in scores for T2DM risk [89][90]. In addition, Mendelian randomization studies showed that HDL-C elevation is associated with a lower risk of developing T2DM [91][92]. Moreover, both HDL particle size and the concentration of large HDL particles were inversely associated with incident T2DM in the general population [4]. Moreover, CETP inhibitors, which increased HDL-C concentration of 29 to 132% in large interventional studies, reduced the risk of new-onset diabetes by 16% on average [93].

Many of the antidiabetic mechanisms induced by HDLs or apoA-I have now been identified [94]. Infusions of rHDLs and apoA-I stimulate insulin secretion and reduce plasma glucose concentrations in obese mice and in T2DM patients [95][96]. From a mechanistic point of view, apoA-I enhances the expression of key enzymes involved in insulin maturation in β-cells [97]. In addition, HDLs protect β-cells from apoptosis induced by endoplasmic reticulum stressors [98].

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