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Contents

Monthly Volume 14 Number 3 March 15, 2023

REVIEW

130 Pancreatic β-cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress

Dludla PV, Mabhida SE, Ziqubu K, Nkambule BB, Mazibuko-Mbeje SE, Hanser S, Basson AK, Pheiffer C, Kengne AP

MINIREVIEWS

147 Role of selenium in type 2 diabetes, insulin resistance and insulin secretion

Casanova P, Monleon D

159 Carbamylated lipoproteins in diabetes

Denimal D

170 AT1 receptor downregulation: A mechanism for improving glucose homeostasis

Lopez DL, Casillas OE, Jaramillo HJ, Romero-Garcia T, Vazquez-Jimenez JG

179 Gestational diabetes mellitus: The optimal time of delivery

Li X, Li TT, Tian RX, Fei JJ, Wang XX, Yu HH, Yin ZZ

188 Fixed-ratio combinations of basal insulin and glucagon-like peptide-1 receptor agonists as a promising strategy for treating diabetes

Nomoto H

198 Multiple influences of the COVID-19 pandemic on children with diabetes: Changes in epidemiology, metabolic control and medical care

Zucchini S, Scozzarella A, Maltoni G

ORIGINAL ARTICLE

Basic Study

209 miR-124 is upregulated in diabetic mice and inhibits proliferation and promotes apoptosis of high-glucose-induced β-cells by targeting EZH2

Duan XK, Sun YX, Wang HY, Xu YY, Fan SZ, Tian JY, Yu Y, Zhao YY, Jiang YL

222 N^{ε}-(carboxymethyl)lysine promotes lipid uptake of macrophage *via* cluster of differentiation 36 and receptor for advanced glycation end products

Wang ZQ, Yao HP, Sun Z

234 Tongxinluo promotes endothelium-dependent arteriogenesis to attenuate diabetic peripheral arterial disease

Gu JJ, Hou YL, Yan YH, Li J, Wei YR, Ma K, Wang XQ, Zhang JH, Wang DD, Li CR, Li DQ, Sun LL, Gao HL

255 Characterization of gut microbial and metabolite alterations in faeces of Goto Kakizaki rats using metagenomic and untargeted metabolomic approach

Zhao JD, Sun M, Li Y, Yu CJ, Cheng RD, Wang SH, Du X, Fang ZH

World Journal of Diabetes

Monthly Volume 14 Number 3 March 15, 2023

Contents

Retrospective Study

271 Clinical and biochemical predictors of intensive care unit admission among patients with diabetic ketoacidosis

Khan AA, Ata F, Iqbal P, Bashir M, Kartha A

Clinical Trials Study

279 Postprandial glucagon-like peptide 1 secretion is associated with urinary albumin excretion in newly diagnosed type 2 diabetes patients

Song LL, Wang N, Zhang JP, Yu LP, Chen XP, Zhang B, Yang WY

Observational Study

290 Prevalence of type 2 diabetes mellitus in the pediatric population of a third-level care hospital in Mexico City in 2013 and 2018

Molina-Díaz JM, Vargas-Terrez BE, Medina-Bravo PG, Martínez-Ambrosio A, Miranda-Lora AL, Klünder-Klünder M

299 Glucose metabolism continuous deteriorating in male patients with human immunodeficiency virus accepted antiretroviral therapy for 156 weeks

Liu DF, Zhang XY, Zhou RF, Cai L, Yan DM, Lan LJ, He SH, Tang H

META-ANALYSIS

313 Effectiveness and safety of traditional Chinese medicine decoction for diabetic gastroparesis: A network meta-analysis

Zhang YX, Zhang YJ, Miao RY, Fang XY, Wei JH, Wei Y, Lin JR, Tian JX

LETTER TO THE EDITOR

343 Ca^{2+}/cAMP ratio: An inflammatory index for diabetes, hypertension, and COVID-19

Bergantin L

347 Successful lifestyle modifications may underlie umbilical cord-mesenchymal stromal cell effects in type 2 diabetes mellitus

Papadopoulou A, Papadopoulos KI

World Journal of Diabetes

Monthly Volume 14 Number 3 March 15, 2023

Contents

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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Carbamylated lipoproteins in diabetes

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Abstract

Diabetic dyslipidemia is characterized by quantitative and qualitative abnormalities in lipoproteins. In addition to glycation and oxidation, carbamylation is also a post-translational modification affecting lipoproteins in diabetes. Patients with type 2 diabetes (T2D) exhibit higher levels of carbamylated low-density lipoproteins (cLDL) and high-density lipoproteins (cHDL). Accumulating evidence suggests that cLDL plays a role in atherosclerosis in diabetes. cLDL levels have been shown to predict cardiovascular events and all-cause mortality. cLDL facilitates immune cell recruitment in the vascular wall, promotes accumulation of lipids in macrophages, and contributes to endothelial dysf-unction, endothelial nitric oxide-synthase (eNOS) inactivation and endothelial repair defects. Lastly, cLDL induces thrombus formation and platelet aggregation. On the other hand, recent data have demonstrated that cHDL serum level is independently associated with all-cause and cardiovascular-related mortality in T2D patients. This relationship may be causative since the atheroprotective properties of HDL are altered after carbamylation. Thus, cHDL loses the ability to remove cholesterol from macrophages, to inhibit monocyte adhesion and recruitment, to induce eNOS activation and to inhibit apoptosis. Taken together, it seems very likely that the abnormalities in the biological functions of LDL and HDL after carbamylation contribute to atherosclerosis and to the elevated cardiovascular risk in diabetes.

Key Words: Carbamylation; Lipoprotein; Diabetes; Low-density lipoprotein; High-density lipoprotein; Myeloperoxidase

Core Tip: There is growing evidence that carbamylation of lipoproteins occurring in diabetes contributes to the pathophysiology of atherosclerosis, and therefore plays a role in the cardiovascular risk. Numerous studies have demonstrated that carbamylated low-density lipoproteins (LDL) is more atherogenic than native LDL, citing, for instance, its role in foam cell formation or ability to damage endothelial function. In addition, carbamylated high-density lipoproteins exhibits reduced antiatherogenic properties, especially in terms of the capacity to induce cholesterol efflux from macrophages and to protect endothelium.

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INTRODUCTION

The excess of cardiovascular risk in patients with type 1 (T1D) or type 2 diabetes (T2D) is multifactorial. Dyslipidemia is a major contributor to this increased cardiovascular risk. It is characterized by quantitative abnormalities of lipoproteins, and also by kinetic, qualitative and functional alterations, that make lipoproteins more atherogenic (reviewed in[1,2]). From a quantitative point of view, T2D patients typically exhibit low serum levels of high-density lipoprotein (HDL)-cholesterol, postprandial hyperlipemia, and hypertriglyceridemia, mainly due to increased very low-density lipoproteins (VLDL). In contrast, most T1D patients only have quantitative lipoprotein abnormalities if they have poor glycemic control.

In addition to these quantitative changes, lipoproteins also undergo post-translational modifications in diabetes, such as glycation, oxidation, acetylation and carbamylation, and also alterations in their lipid and protein composition. These changes give them a more atherogenic profile overall, and therefore may likely contribute to the increased cardiovascular risk in diabetes. In this review, we will focus on one of these post-translational modifications affecting lipoproteins in diabetes, namely carbamylation. Carbamylation (carbamoylation *stricto sensu*) is a non-enzymatic irreversible process mediated by isocyanate, and corresponds to the binding of a carbamoyl moiety (-$CONH_2$) to lysine, resulting in carbamyllysine (CML) (Figure 1). Thus, carbamylation affects the protein part of lipoproteins, primarily apolipoproteins (apo), but also other proteins. Isocyanate originates from either the spontaneous dissociation of urea, or from the myeloperoxidase (MPO)-catalyzed oxidation of thiocyanate, or to a lesser extent, from tobacco smoke or atmospheric pollution.

MPO is secreted mainly by neutrophils and monocytes at inflammatory sites including atherosclerotic plaques. It colocalizes with carbamylated proteins in human atherosclerotic lesions, and serves as a dominant pathway for promoting carbamylated proteins in atherosclerotic plaques[3]. The role of MPO in cyanate production suggests that, beyond uremia and chronic kidney disease (CKD), lipoprotein carbamylation may be also driven by inflammation, which is obviously a major phenomenon in atherosclerosis and diabetes. It has been well demonstrated that plasma MPO is increased in T1D[4-6] and T2D [7,8] diabetes. Plasma MPO level is associated with the presence of coronary artery disease[9], and above all predicts coronary artery disease[10] and cardiovascular events[11]. It should be noted right away that MPO also produces hypochlorous acid ($HOCl^-$) and peroxynitrite in addition to cyanate in atherosclerotic plaques, which can lead to lipoprotein changes other than carbamylation such as chlorination and nitration.

Accumulating evidence from *in vitro*, epidemiological, animal and human studies emphasizes an emerging role for carbamylation in atherosclerosis and diabetes. For instance, plasma levels of protein-bound CML have been shown to be independently and positively associated with the frequency of patients having cardiovascular diseases, and to predict the risk of major adverse cardiac events in the following 3 years[3]. In this review, we will focus on the role of carbamylated LDL (cLDL) and HDL (cHDL) in the pathophysiology of atherosclerosis and diabetes.

CARBAMYLATED LDL

LDL, the major transporter of cholesterol within the blood, is composed of a core of esterified cholesterol enclosed in a monolayer of phospholipids and unesterified cholesterol, together with a single molecule of apoB-100. LDL delivers lipids to peripheral tissues after binding to LDL receptors. Circulating LDL particles are able to penetrate the endothelium of arterial walls and on entrance they become oxidized, and promote endothelial dysfunction, inflammation and foam cell formation. Serum LDL-cholesterol level is an independent risk factor for cardiovascular events, and lowering it is a major goal of dyslipidemia management in current guidelines.

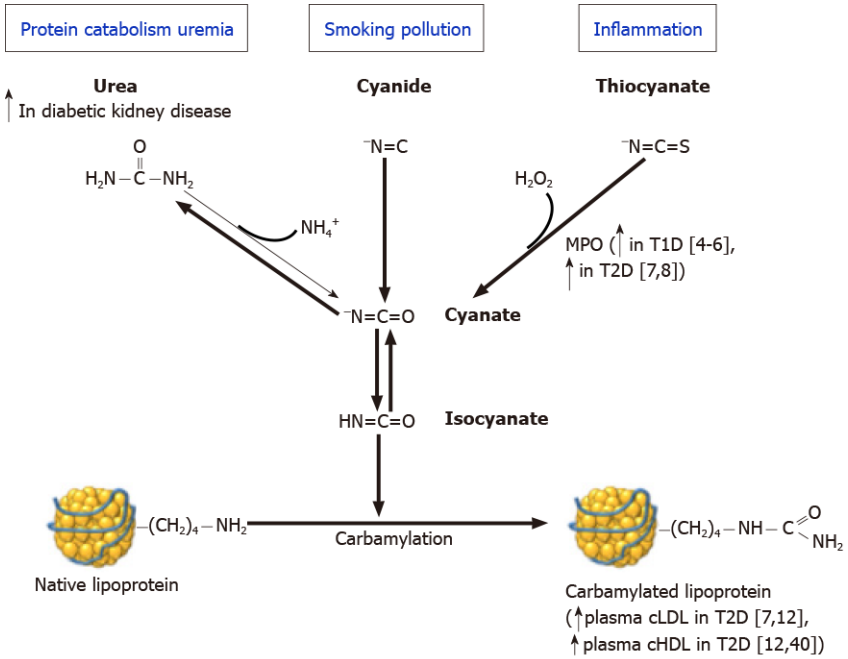

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Figure 1 Carbamylation of lipoproteins is a non-enzymatic irreversible process mediated by isocyanate, and corresponds to the irreversible binding of a carbamoyl moiety to ε-NH_2 of lysine residues in proteins, resulting in carbamyllysine. Isocyanate originates from either the non-enzymatic spontaneous dissociation of urea, or from the myeloperoxidase (MPO)-mediated oxidation of thiocyanate, or to a lesser extent from tobacco smoke or atmospheric pollution. The urea pathway is of particular relevance in diabetic patients with chronic kidney disease. MPO level is elevated in patients with type 1 and type 2 diabetes (T2D). Plasma levels of carbamylated low-density lipoproteins and high-density lipoproteins are increased in T2D patients with or without chronic kidney disease. T2D: Type 2 diabete; CML: Carbamyllysine; MPO: Myeloperoxidase; Lys: Lysine; cLDL: Carbamylated low-density lipoproteins; cHDL: Carbamylated high-density lipoproteins.

Beyond oxidation, LDL is also subject to carbamylation in diabetes, and it has been shown that patients with T2D[7,12] or metabolic syndrome[13], including those without CKD, exhibit higher levels of cLDL than healthy individuals. This increase is heightened even more in T2D patients with renal impairment[12]. MPO plays a major role in LDL carbamylation at inflammatory sites such as atherosclerotic lesions in diabetes. This is corroborated by the fact that plasma MPO is correlated with plasma cLDL levels in T2D patients[7]. To date, no data are available on cLDL levels in patients with T1D to our knowledge.

Numerous evidence supports the hypothesis that cLDL is more atherogenic than native LDL, and thus is likely to contribute to the increased cardiovascular risk in diabetes. At an epidemiological level, cLDL levels are predictive of cardiovascular events and all-cause mortality in patients with CKD[14]. At a cellular and molecular levels, numerous studies have shown that cLDL promotes atherosclerosis (Figure 2). First, it should be noted that cLDL shows greater accumulation in aortic subendothelial space more than native LDL[15]. In addition, cLDL is found in the aortic wall of apoE-null mice, and colocalizes with macrophage infiltration in aortic walls and atherosclerotic plaques[16]. Interestingly, the clearance of cLDL from human and rabbit plasma is modulated by the degree of carbamylation[17,18], suggesting a longer residence time in subendothelial space.

Excessive deposition of cholesterol within arterial vessels and the development of foam cells are key features of atherosclerosis. Foam cells are derived mostly from macrophages that take up modified lipoproteins and lipoprotein-immune complexes. The various uptake mechanisms include scavenger receptors (SR) that are important particularly in the uptake of oxidized LDL (oxLDL). Several SR bind modified LDL, and are involved in the development and stability of atherosclerotic plaques, by initiating signaling cascades that regulate macrophage activation, lipid metabolism, and inflammation. It is now well established that SR-A1, SR-B2 (*i.e.*, CD36) and SR-E1 [*i.e.*, lectin-like-oxLDL receptor-1 or lipoprotein receptor-1 (LOX-1)], all expressed by multiple cell types in arterial tissue, are activated by the binding of oxLDL[19]. It has been shown that cLDL, like oxLDL, is more efficient than native LDL at inducing the accumulation of lipids in murine macrophages and promoting foam cell formation[3,20]. This effect appears to be mediated by the activation of SR. In fact, cLDL is able to bind to SR-A1, CD36, and LOX-1[15,20]. SR-A1 seems to play a crucial role in the effects of cLDL effects, because mice lacking SR-A1 are not prone to cholesterol accumulation and foam cell formation, and blockage of SR-A1 by an antibody reduces foam cell formation in murine macrophage cell cultures[3,20]. The inhibition of LOX-1 by an antibody also reduces foam cell formation, suggesting that this receptor also has a pivotal role in the effects of cLDL effects on macrophages[20]. The role of CD36 remains unclear, since cLDL-induced

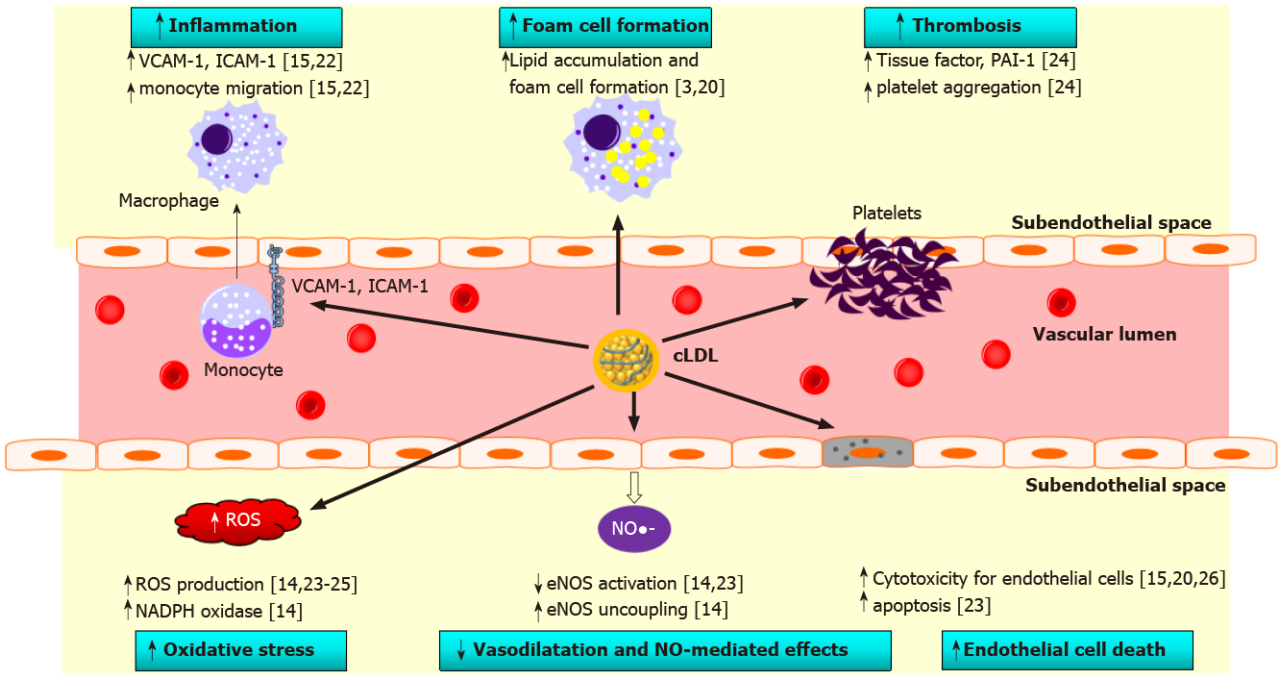

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Figure 2 Role of carbamylated low-density lipoproteins in atherosclerosis. Carbamylated low-density lipoproteins (cLDL) facilitates immune cell recruitment in the subendothelial space by increasing the expression of adhesion molecules vascular cell adhesion molecule-1 and intercellular adhesion molecule-1. It also promotes accumulation of lipids in macrophages and thus facilitates foam cell formation. cLDL induces platelet aggregation and thrombus formation associated with a higher activity of tissue factor and plasminogen activator inhibitor type 1. In addition, cLDL activates NAPDH oxidase and increases the production of reactive oxygen species. cLDL are less efficient than native LDL at activating endothelial nitric oxide synthase. Lastly, cLDL is cytotoxic for endothelial cells. VCAM-1: Vascular cell adhesion molecule-1; ICAM-1: Intercellular adhesion molecule-1; PAI-1: Plasminogen activator inhibitor type 1; cLDL: Carbamylated low-density lipoproteins; ROS: Reactive oxygen species; eNOS: Endothelial nitric oxide synthase.

foam cell formation is attenuated by an anti-CD36 antibody in murine macrophage cell cultures[20], whereas mice lacking CD36 are not more subjects to cholesterol accumulation and foam cell formation [3]. Furthermore, cLDL are less well recognized by the LDL receptor than native LDL[3,18,21].

The adhesion of monocytes to endothelium and their migration into the intima are major steps in the initiation and progression of atherosclerosis. Next, monocytes differentiate into macrophages in the arterial wall, and are prone to becoming foam cells under proatherogenic conditions. The recruitment of monocytes into the intima is triggered by an increased production of chemotactic factors in vessels such as monocyte chemoattractant protein (MCP)-1 (*i.e.*, C-C motif chemokine ligand 2), and also by an upregulation of adhesion molecules on endothelial cells, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and selectins. It has been shown that cLDL facilitates monocyte adhesion to endothelial cells by increasing VCAM-1 and ICAM-1 expression on endothelial cells[15,22]. However, cLDL does not modify P-selectin expression and MCP-1 production in endothelial cells[22]. The LOX-1 receptor seems to be involved in the monocyte adhesion induced by cLDL, in contrast to SR-A1 and CD36[15]. A vicious circle could be set up since cLDL induces LOX-1 expression in endothelial cells[15,23].

More broadly, cLDL promotes endothelial dysfunction, which is a cornerstone of atherosclerosis development. *Ex-vivo* experiments have shown that cLDL impairs endothelium-dependent relaxation of murine aortic rings[14]. From a mechanistic point of view, cLDL activates LOX-1 receptor and its effector p37-MAPK, thus activating NADPH-oxidase in endothelial cells[14]. Indeed, cLDL has been shown to induce more oxidative stress and reactive oxygen species (ROS) than native LDL in human umbilical vein endothelial cells (HUVEC)[23], human aortic endothelial cells[14], murine aortic rings [14], murine aorta and blood[24], and in human endothelial progenitor cells[25]. Enhanced production of ROS is known to reduce the bioavailability of endothelium-derived nitric oxide (NO), contributing to endothelial dysfunction. Thus, cLDL leads to reduced activating phosphorylation of endothelial NO-synthase (eNOS) at serine 1177[14,23], and to increased eNOS phosphorylation at the inhibitory site threonine 495[14]. cLDL also facilitates eNOS uncoupling[14], which in turn could contribute to increased ROS production. cLDL-induced eNOS uncoupling could be at least partially due to S-glutathionylation of eNOS[14].

cLDL is cytotoxic for human endothelial cells[15,20,26], and it induces more apoptosis than native LDL[23,26,27]. LOX-1 receptor plays a role since its downregulation using a small interfering RNA strongly attenuates cLDL-induced apoptosis in HUVEC[23]. In addition, the cLDL-induced cytotoxic effect on endothelial cells is at least partially mediated by endonuclease G, a nuclease implicated in

caspase-independent cell death *via* DNA fragmentation[27]. Moreover, cLDL induces autophagy in human coronary artery endothelial cells[28]. cLDL accelerates senescence in human endothelial progenitor cells, which may play a role in the failure to repair endothelial damage in atherosclerosis [25]. One study has shown that cLDL induces endothelial cell proliferation, leading to more cell death than native LDL, through the mitogen-activated protein kinase MAPK ERK1/2 pathway[29].

Although vascular smooth muscle cells (VSMC) play a complex role in atherosclerosis, VSMC and VSMC-derived cells are recognized to be a major source of plaque cells and extracellular matrix at all stages of atherosclerosis. It has been well demonstrated that cLDL induces a marked proliferation of VSMC[3,26,30]. However, cLDL has no cytotoxic effects on VSMC or on extracellular matrix protein synthesis by VSMC[30]. In addition, cLDL enhances migration of VSMC by the increasing the expression of LR11, a member of the LDL receptor family highly expressed in VSMC of the intima[31]. Lastly, cLDL increases VCAM-1 and ICAM-1 expression on VSMC[30], which could facilitate immune cell recruitment in the arterial wall.

Thrombus formation on disrupted atherosclerotic plaques or arterial erosions promotes the development of atherosclerotic lesions and frequently causes acute coronary syndrome. It has been elegantly shown that human cLDL administered to mice accelerates arterial thrombus formation compared to native LDL[24]. The underlying mechanisms could be a higher activity of tissue factor and plasminogen activator inhibitor type 1 through a LOX-1-dependent mechanism[24]. Moreover, cLDL enhances platelet aggregation *in vitro*[24].

Lastly, it has been suggested that cLDL may be involved in the pathogenesis of T2D by facilitating insulin resistance. Indeed, cLDL attenuates glucose uptake and decreases glucose transporter type 4 membrane expression *via* NO mediated tyrosine nitration of insulin receptor substrate-1 in rat muscle cells[32].

CARBAMYLATED HDL

HDL is a heterogeneous lipoprotein in terms of its size, density and lipid and protein composition. ApoA-I is the major functional and structural protein. HDL is well known to protect against atherosclerosis by its preponderant role in the removal of excess cholesterol from the vascular wall. In addition, HDL also exhibits anti-inflammatory, anti-oxidative, anti-thrombotic and endothelium protection properties.

HDL undergoes modifications at sites of inflammation and within atherosclerotic lesions, disrupting their antiatherogenic effects (reviewed in[33]). HDL is prone to be carbamylated within the subendothelial space[34,35], and apoA-I isolated from human atherosclerotic lesions is largely more carbamylated than total proteins in plasma[36]. In addition, HDL isolated from human atherosclerotic lesions of the abdominal aorta has been demonstrated to be largely more carbamylated than in plasma [34,35]. The relative contribution of the enzymatic (thiocyanate/MPO system) and the non-enzymatic (cyanate) pathways in HDL carbamylation is a matter of debate. It has been shown that MPO is associated with HDL within human atheroma[37], and that apoA-I is a selective target for MPO within atherosclerotic lesions[37]. MPO induces the carbamylation of lipid-poor apoA-I[36], a fact that is particularly relevant because the majority of apoA-I within aortic tissue is in lipid-free and lipid-poor forms [38]. It has been observed that MPO-induced modifications of HDL, such as the formation of 3-chlorotyrosine (a specific fingerprint of MPO oxidation), is particularly elevated in human atherosclerotic intima[39]. In addition, the 3-chlorotyrosine content of HDL correlates significantly with the CML content[35]. In addition, the CML content of HDL from T2D patients correlates with MPO concentration [40]. All these data taken together suggest that the carbamylation of HDL is largely mediated by MPO.

It has been observed that T2D patients (with or without CKD) have higher levels of cHDL than healthy individuals[12,40]. Moreover, cHDL levels are higher in T2D patients with coronary artery disease than in those without coronary artery disease[40]. Very interestingly, a recent prospective study has shown that cHDL serum level in T2D patients is independently associated with all-cause and cardiovascular-related mortality after a median follow-up of 14 years[41]. Furthermore, cHDL level seems to be associated with renal outcomes in T2D, since it has been recently shown to predict CKD progression in T2D patients[12]. This observation could be in line with previous data suggesting that alterations of HDL metabolism may be associated with renal outcomes in T2D, since HDL-cholesterol level is an independent risk factor for the development of kidney microvascular disease[42].

In T1D, data on cHDL levels are more scarce, although it has been demonstrated that plasma MPO activity is increased compared to non-diabetic individuals[4-6]. Our group recently showed that a standard intervention to improve glycemic control in T1D patients decreased cHDL levels[43]. That was independently associated with an improved cholesterol efflux capacity[43], which is now well recognized as a predictor of cardiovascular events.

One of the well-known properties of HDL is its ability to promote cholesterol efflux from lipid-laden macrophages using the transporters ATP-binding cassette transporter A1 (ABCA1), ATP-binding cassette transporter G1 and SR-BI, and as a carrier for its excretion. Over the past few years, research has demonstrated that the ability of HDL to promote cholesterol efflux is more strongly inversely associated

with incident cardiovascular events than circulating HDL cholesterol level[44,45]. Several findings suggest that carbamylation of HDL alters its atheroprotective properties (Figure 3). Our group and others have shown that carbamylation of HDL[35,43] or apoA-I[46] alters its ability to promote cholesterol efflux in human macrophages. Carbamylation reduces the ability of HDL to promote SR-BI-dependent cholesterol efflux in macrophages, but the carbamylation of apoA-I has no effect on ABCA1-mediated cholesterol uptake[35]. This result could be due to a change in the affinity of cHDL for SR-BI in macrophages[35]. Lecithin-cholesterol acyltransferase (LCAT), which is involved in the maturation of spherical HDL and in the initial step of reverse cholesterol transport, is less active in cHDL[34].

In addition, cHDL has altered protective effects on endothelium. Endothelial repair plays a crucial role in the prevention of vascular disease by maintaining the integrity of the endothelium. The ability of cHDL to stimulate migration, angiogenesis and proliferation is reduced in human aortic endothelial cells compared to native HDL[47]. cHDL decreases vascular endothelial growth factor receptor-2 and SR-BI levels, and subsequently affects the PI3K/Akt downstream pathway in human aortic endothelial cells, all of which being involved in endothelial repair[47]. This downregulation of the capacity for endothelial repair induced by cHDL is likely to contribute to endothelial dysfunction in diabetes. Paraoxonase-1 (PON-1) activity was found to be inversely correlated with cHDL level in end-stage renal disease[47]. cHDL loses its antiapoptotic activity on human coronary artery endothelial cells[3].

HDL particles have also anti-inflammatory functions. Very recently, an inverse association between the anti-inflammatory capacity of HDL and incident cardiovascular events has been established in a general population cohort, independently of both HDL cholesterol level and cholesterol efflux capacity [48]. Many studies suggest that the anti-inflammatory properties of HDL are altered by its carbamylation. Thus, cHDL promotes the adhesion of monocytes to HUVEC in a dose-dependent manner [40]. The carbamylation of HDL or of recombinant HDL reduces its ability to inhibit the tumor necrosis factor α-induced expression of VCAM-1, ICAM-1 and E-selectin in human coronary endothelial cells[40,46]. The mechanism implies an upregulation of the nuclear factor-kappaB/p65 pathway[40], which plays an important role in the regulation of adhesion molecules.

Under physiological conditions, HDL is able to activate eNOS and therefore to stimulate NO production by the endothelium. This contributes to some beneficial effects of HDL such as vasorelaxation or the inhibition of different factors that promote atherosclerosis progression[49]. We and others have found that HDL is less efficient at inducing NO production in endothelial cells in patients with T2D[50] or metabolic syndrome[51]. We showed that sphingosine-1-phosphate depletion of HDL is the main factor responsible for this defect in metabolic syndrome[51]. To our knowledge, no direct evidence to date demonstrates that cHDL is less efficient at inducing NO production. However, HDL modified by HOCl, another MPO product besides cyanate, was less efficient at activating eNOS, with associated changes in eNOS intracellular distribution[52]. MPO/HOCl induces the formation in HDL of 2-chlorohexadecanal from HDL-associated plasmalogens, and this lipid has been shown to inactivate eNOS[52]. Interestingly, we have reported that HDL was depleted in plasmalogens from patients with T1D[53], T2D[54] and metabolic syndrome but without diabetes[55], and that could be an indirect marker of MPO/HOCl action on HDL particles.

HDL contributes to protecting LDL from oxidation. Plasmalogens and the HDL-associated proteins LCAT and PON-1 are involved in the anti-oxidant properties of HDL. The carbamylation of HDL reduces its ability to inhibit radical-induced LDL oxidation[34]. The carbamylation of LCAT and PON-1 could explain this alteration, since it has been shown that PON-1 is prone to carbamylation[56], and above all that the activity of both LCAT and PON-1 is decreased in cHDL[34].

CONCLUSION

We have summarized here the main data on lipoprotein carbamylation in diabetes and on its potential role in the development of atherosclerosis. There is now accumulating evidence suggesting that cLDL plays a role in atherosclerosis, as oxLDL has been known for a long time. For example, it has been demonstrated that cLDL promotes foam cell formation, immune cell recruitment in the vascular wall, eNOS inactivation and uncoupling and endothelial repair defects. HDL, on the other hand, has altered atheroprotective properties after carbamylation. cHDL loses the ability to remove cholesterol from macrophages, to inhibit monocyte adhesion and recruitment, to induce eNOS activation and also to inhibit apoptosis. Taken together, this means it is very likely that these abnormalities in the biological functions of LDL and HDL after carbamylation contribute to atherosclerosis and to the increased cardiovascular risk in diabetes.

Minimizing the carbamylation of lipoproteins therefore appears to be a relevant approach in the management of diabetes to reduce cardiovascular risk. Above all else, smoking (a well-known source of cyanate) cessation is obviously a significant action to reduce lipoprotein carbamylation, and in general to decrease cardiovascular risk. Moreover, we must keep in mind that more than 40% of people with diabetes are likely to develop CKD[57]. Therefore, the prevention of CKD and subsequent elevated uremia trough the usual care is also a way to prevent lipoprotein carbamylation in diabetic patients. Our group recently showed that conventional treatment to improve glycemic control in uncontrolled

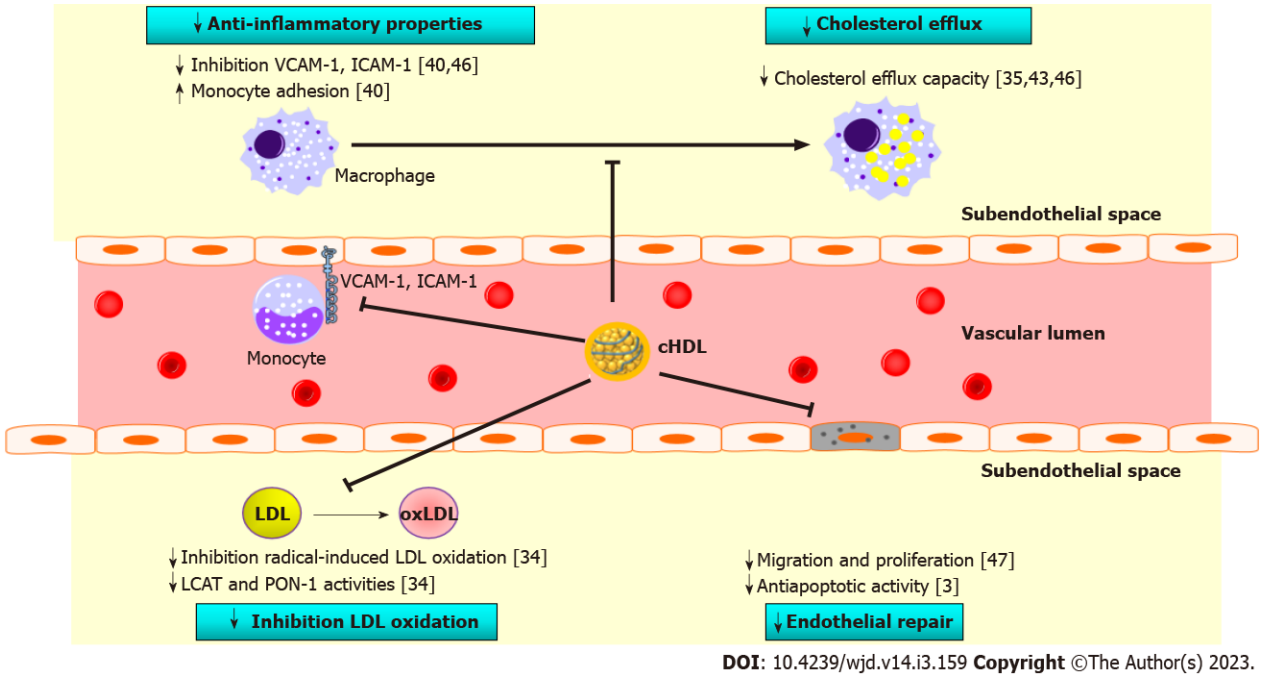

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Figure 3 Role of carbamylated high-density lipoproteins in atherosclerosis. The atheroprotective properties of high-density lipoproteins (HDL) are altered after carbamylation. Thus, carbamylation HDL (cHDL) partially loses its ability to remove cholesterol from macrophages and to inhibit monocyte adhesion. cHDL is less able to protect low-density lipoproteins from oxidation, likely due to reduced lecithin-cholesterol acyltransferase and paraoxonase-1 activities. Lastly, cHDL has an impaired capacity to facilitate endothelial repair. VCAM-1: Vascular cell adhesion molecule-1; ICAM-1: Intercellular adhesion molecule-1; PAI-1: Plasminogen activator inhibitor type 1; LDL: Low-density lipoproteins; LCAT: Lecithin-cholesterol acyltransferase; PON-1: Paraoxonase-1; cHDL: Carbamylation high-density lipoproteins.

T1D patients is accompanied by a decrease in cHDL, despite the lack of a clear mechanistic explanation [43].

The inhibition of MPO could also be a promising strategy to inhibit the formation of carbamylated lipoproteins[58,59]. However, it should be kept in mind that MPO plays a role in innate immunity, and such an approach must be thoroughly evaluated regarding infection risk. The nuclear receptor peroxisome proliferator-activated receptor (PPAR)-gamma regulates MPO expression in macrophages [60]. Interestingly, it has been demonstrated that the PPAR-gamma agonist rosiglitazone decreases MPO expression and activity in neutrophils from hypercholesterolemic rabbits[61], and that it lowers plasma cLDL and MPO levels in T2D patients with normal renal function[7]. Infusion of apoA-I or recombinant HDL resistant to carbamylation could be an interesting strategy in diabetic patients with cardiovascular events. This could theoretically be made by substituting relevant MPO/cyanate-targeted lysine residues of apoA-I, by analogy with what was done with the apoA-I variant 4WF, which is made resistant to MPO-induced oxidation by replacing four tryptophan residues with phenylalanine[62,63]. Another innovative strategy is the local delivery of adeno-associated viral vectors expressing *apoA1* variants using endovascular stenting[64]. Finally, antioxidants could counteract the increased ROS production and MPO-mediated oxidation of lipoproteins in diabetes. Ascorbic acid (vitamin C), α-tocopherol (vitamin E) and above all lycopene have been shown to inhibit LDL carbamylation *in vitro*[65].

In addition, it has been hypothesized that ornithine may be able to compete with ε-amino groups of lysine residues found in apolipoproteins in their binding to isocyanate, leading to a decrease in cLDL formation[66]. Finally, it has been shown that flavonoids are able to inhibit LDL carbamylation (probably by scavenging cyanate ions)[67].

To conclude, increasing the knowledge of lipoprotein abnormalities in diabetes is important to better understand the pathophysiology of diabetic dyslipidemia, and to develop new therapeutic strategies to reduce cardiovascular risk. As far as carbamylation is concerned, recent studies suggest that carbamylated lipoproteins likely play a causative role in atherosclerosis, beyond simply being a biomarker of cardiovascular risk in patients with diabetes.

FOOTNOTES

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