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EDITORIAL

High density lipoproteins and type 2 diabetes: Emerging concepts in their relationship

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Abstract

Patients with type 2 diabetes mellitus (T2DM) frequently exhibit macrovascular complications of atherosclerotic cardiovascular (CV) disease. High density lipoproteins (HDL) are protective against atherosclerosis. Low levels of HDL cholesterol (HDL-C) independently contribute to CV risk. Patients with T2DM not only exhibit low HDL-C, but also dysfunctional HDL. Furthermore, low concentration of HDL may increase the risk for the development of T2DM through a decreased β cell survival and secretory function. In this paper, we discuss emerging concepts in the relationship of T2DM with HDL.

Key words: Type 2 diabetes; High density lipoproteins; Insulin secretion; β cells; Paraoxonase-1

Core tip: Patients with type 2 diabetes mellitus (T2DM) not only exhibit low high density lipoprotein (HDL) cholesterol, but also dysfunctional HDL. Furthermore, low concentration of HDL may increase the risk for the development of T2DM through a decreased β cell survival and secretory function. In this paper, we discuss emerging concepts in the relationship of T2DM with HDL.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) affects approximately 12 million people in the United States[1]. Atherosclerotic cardiovascular (CV) disease accounts for about 70% of overall mortality in patients with T2DM[2,3]. Various factors, modifiable or not, promote atherosclerosis in these patients[1]. These include metabolic abnormalities, such as hyperglycemia, hyperinsulinemia, albuminuria and atherogenic dyslipidemia [low high density lipoprotein cholesterol (HDL-C) together with increased triglycerides (TG) levels, as well as raised cholesterol concentration of the small dense low density lipoprotein (sdLDL) particles][1,4-7].

Atherogenic dyslipidemia is characterized by the imbalance between pro-atherogenic apolipoprotein (apo)B-containing and anti-atherogenic apoA1-containing lipoprotein particles[8]. In this context, sdLDL particles predominate[9-13]. The small size of LDL particles has been recognized as a risk predictor of CV events[10,11,14].

Interestingly, the risk of coronary heart disease (CHD) associated with atherogenic dyslipidemia may exceed the risk from raised low density lipoprotein cholesterol (LDL-C) levels of 150-220 mg/dL[1,7]. Furthermore, even statin-treated patients with T2DM within LDL-C goals exhibit residual CV risk, which is partially associated with the presence of atherogenic dyslipidemia[15,16]. A *post hoc* analysis of the United Kingdom Prospective Diabetes Study (UKPDS) assessed the CV risk across quintiles of log(TG)/HDL-C in 585 men with T2DM[17]. The risk for CHD or cerebrovascular events was augmented at the highest compared with the lowest quintile (28% *vs* 52%,

respectively, $P = 0.001$)[17].

Except for the predominance of sdLDL particles, low HDL-C levels comprise an independent risk factor of CV events[18,19]. In the Framingham Heart Study, HDL-C was a more potent predictor of CHD than total cholesterol, LDL-C or TG[18]. It was suggested that for every 1 mg/dL decrease in HDL-C levels, the risk for CHD increases by 2% in men and 3% in women[20].

HDL is responsible for the process of reverse cholesterol transport from peripheral tissues, including arterial wall, to the liver[21]. Furthermore, HDL exhibits multiple anti-atherogenic actions[21,22]. These include anti-inflammatory, anti-oxidant and anti-thrombotic effects together with an HDL-associated restoration of endothelial function[21,22]. These actions are mediated at least in part by the enrichment of HDL with apoA1 or enzymes [*e.g.,* paraoxonase-1 (PON1) and HDL-associated lipoprotein-associated phospholipase A_2 (Lp-PLA_2)][21,23,24]. In this paper, we discuss the relationship between T2DM and HDL.

LOW LEVELS OF HDL-C IN T2DM

Patients with T2DM exhibit low HDL-C levels[12]. Among 7692 outpatients with T2DM, the prevalence of low HDL-C levels (< 40 and 50 mg/dL for men and women, respectively) was 49.5%[25]. Several mechanisms have been described to explain this abnormality mostly associated with the predominance of TG-rich lipoproteins[12,23,26]. Briefly, very low density lipoproteins (VLDL) are overproduced in insulin resistant states[12,23,26]. Furthermore, insulin resistance is associated with a defective clearance of TG-rich lipoproteins (*i.e.,* VLDL, chylomicrons and their remnants) *via* lipoprotein lipase (LPL)[23]. These lipoproteins exchange their core lipids with HDL through cholesterol ester transfer protein (CETP) resulting in TG-enriched HDL particles[27]. The activity of CETP is enhanced in insulin resistant states (*e.g.,* T2DM)[27]. The enrichment of HDL particles with TG decreases the stability and plasma residence time of these lipoproteins[23,28,29]. Namely, apoA1 is easily removed from circulating TG-rich HDL particles following lipolysis[23,28]. Furthermore, the lipolysis of these lipoproteins by hepatic lipase gives rise to small HDL particles, which are rapidly cleared[23,28]. Also, hypertriglyceridemic states are characterized by reduced availability of the lipolytic surface fragments derived from TG-rich lipoproteins. These components are necessary for the formation of HDL[23,28].

DYSFUNCTIONAL HDL IN T2DM

It was suggested that HDL is dysfunctional in T2DM. Experimental *in vivo* and *in vitro* studies showed that HDL-associated reverse cholesterol transport is impaired in T2DM[30-32]. Several mechanisms were suggested to mediate this abnormality. These include a reduced expression of the ATP-binding cassette (ABC) transporters. The members A1 and G1 of this family facilitate the efflux of cellular free cholesterol and phospholipid to assemble with apoA1 and form nascent HDL[33]. The gene expression and protein levels of ABC-A1 were reduced in T2DM in parallel with poor glycemic control[32]. This may increase risk for CHD[34]. Furthermore, insulin decreased the *in vitro* protein expression and activity of ABC-G1[35]. This finding suggests a role of hyperinsulinemia (*e.g.,* in T2DM) in defective HDL-mediated reverse cholesterol transport.

The oxidative modification of HDL (especially of apoA1) by glycated hemoglobin may be another mechanism explaining HDL dysfunctionality in T2DM[30,31]. This could be related to the presence of the haptoglobin Hp2 allele, which increases the oxidative modification of circulating lipoproteins[31]. Experimental data showed that HDL dysfunctionality in T2DM may be ameliorated by the use of antioxidants (*e.g.,* vitamin E) *in vivo*[36]. Furthermore, the anti-oxidant defense of HDL is decreased in T2DM. This could be associated with a reduced PON1 activity mediated by the glycation of this enzyme[37-39]. Of interest, postprandial glycemia and impaired catabolism of TG-rich lipoproteins was associated with decreased PON1 activity in T2DM[40-42]. Several polymorphisms of *PON1* gene favor the defective action of PON1 in T2DM[43]. Reduced PON1 activity was an independent predictor of CV events in patients with T2DM[44].

We have previously shown that patients with metabolic syndrome exhibit decreased activity of HDL-associated Lp-PLA_2 compared with age and sex-matched controls[45,46]. HDL-associated Lp-PLA_2 contributes significantly to the anti-inflammatory and anti-atherogenic potential of HDL[47,48]. Despite low activity of this enzyme in pre-diabetic insulin resistant states, data are insufficient for patients with T2DM.

PROTECTIVE ROLE OF HDL IN THE PATHOGENESIS OF T2DM

The gradual deterioration of pancreatic β cell function following persistent insulin resistance is the main pathophysiological event in T2DM[49,50]. At the time of T2DM diagnosis, the secretory function of β cells is declined by approximately 50% of normal[51]. It was suggested that lipoproteins may regulate glucose homeostasis by affecting both peripheral insulin resistance and pancreatic islet secretion[52]. For example, high circulating levels of free fatty acids impair insulin sensitivity[53-55]. The emerging concept is that atherogenic dyslipidemia may precede T2DM and favor its development by promoting the dysfunction and apoptosis of β cells[56]. In the UKPDS, the log(TG)/HDL-C ratio, as a surrogate of atherogenic dyslipidemia, was associated with decreased insulin sensitivity and impaired β cell function in 585 male patients with T2DM[17].

Low HDL-C levels independently predict the development of T2DM[57]. A recent observational study investigated the association of HDL-C and β cell function in 1087 subjects at risk of T2DM[58]. Low HDL-C levels

were independently associated with indices of β cell dysfunction in patients with impaired either fasting glucose or glucose tolerance[58].

Pancreatic β cells express receptors that participate in the binding and processing of plasma lipoproteins[53,59]. These include the LDL-receptor and the LDL-receptor related protein[60]. Both circulating and endogenous cholesterol of β cells can affect insulin secretion[60]. In this context, VLDL and LDL particles reduce insulin mRNA expression and proliferation, while inducing apoptosis of β cells[53]. Furthermore, cholesterol accumulation in pancreatic β cells may impair their secretory function[52,60,61]. In contrast, HDL exerts a protective role by improving β cell secretory function and antagonizing the apoptosis of these cells[53]. The lipid-free apoA1 and apoA2 or HDL increased insulin secretion by up to 5-fold *in vitro*[62]. Furthermore, the administration of reconstituted HDL in patients with T2DM improved the glycemic control by increasing β cell insulin secretory function[63].

The process of reverse cholesterol transport can help explain these benefits. Several experimental studies highlighted the protective role of ABC-A1 against T2DM[60]. In contrast, ABC-A1 knockout mice exhibited impaired glucose tolerance due to a decreased insulin secretion upon glucose stimulation[64]. This effect was not accompanied by any changes in insulin mRNA expression, suggesting that cholesterol accumulation in β cells interferes with insulin exocytosis[52,64]. Furthermore, human carriers of loss-of-function ABC-A1 mutations exhibited reduced not only HDL-C levels, but also insulin secretion[63,65]. On the other hand, rosiglitazone improved glucose tolerance by upregulating the expression of ABC-A1 gene[64].

Several *in vitro* studies suggested a beneficial role of HDL on the survival of β cells[53,56,66]. This benefit may be mediated by the anti-oxidant effects of HDL. For example, oxidized LDL (oxLDL) decreased insulin secretion at the transcriptional level and promoted apoptosis of β cells *in vitro*[66]. This was associated with an activation of the Jun N-terminal kinase pathway[66,67]. HDL reversed these actions of oxLDL[66]. To this extent, experimental studies showed that PON1 increases insulin secretion, thereby reducing the incidence of T2DM *in vivo*[68,69]. PON1 was also associated with increased survival of β cells[69]. Furthermore, not only PON1 but also HDL-associated Lp-PLA$_2$ inhibits the oxidation of LDL[70]. Lp-PLA$_2$ is produced in the arterial wall by macrophages[70]. It is associated with lipoproteins, primarily LDL and secondarily HDL, and degrades bioactive phospholipids[70]. Both PON1 and HDL-associated Lp-PLA$_2$ protected hypercholesterolemic mice from atherosclerosis[71,72]. OxLDL inhibit these enzymes[72]. Therefore, oxLDL and HDL are considered antagonists in the development of atherosclerotic vascular disease[72].

CONCLUSION

Interest is increasing on the protective role of HDL against atherosclerotic CV disease. CV risk is high even in patients with T2DM who exhibit LDL-C levels within normal range. Low HDL-C is an independent contributor of this residual risk. The increased concentration of circulating TG-rich lipoproteins mostly accounts for low HDL-C levels in patients with T2DM. Considerable evidence suggests that HDL is dysfunctional in T2DM. Indeed, decreased ABC-A1 and/or -G1 expression reduces biosynthesis of HDL in T2DM through reduced availability of cholesterol for loading to apoA1. This results in impaired reverse cholesterol transport. Furthermore, the oxidative modification of HDL (especially of apoA1) in T2DM impairs its functionality. This is in part associated with a reduced anti-oxidant defense of these lipoproteins *via* PON1. The emerging concept is that low HDL-C may be involved in the pathogenesis of T2DM. The abundance of circulating atherogenic particles together with the increased intracellular cholesterol concentration in β cells have been associated with impaired secretory function of pancreatic islets. HDL by removing cholesterol from these cells may increase insulin secretion. Furthermore, these lipoproteins increase the survival of β cells by mechanisms which are under investigation. The anti-oxidant actions of HDL *via* PON1 may play a key role in this benefit.

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