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Review article

HDL functionality in type 1 diabetes

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ABSTRACT

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by absence of insulin secretion due to destruction of the pancreatic beta-cells. Patients with T1D exhibit an increased risk for cardiovascular disease (CVD) compared with non-diabetic subjects. It has been established that low concentration of high-density lipoprotein cholesterol (HDL-C), an independent risk marker of CVD, coincides with a reduced protective capacity against oxidative stress. However, conflicting results have been reported on the prevalence of low HDL-C levels in T1D. Interestingly, changes in composition and function of HDL particles (abnormal ratio of cholesteryl ester-to-triglyceride, reduction in the phospholipid content, reduced capacity to promote cholesterol efflux from macrophages, impaired anti-inflammatory and anti-oxidant activities) have been described in patients with T1D. Hence, exploring HDL function, even in the presence of normal HDL-C levels, might provide additional insight into the underlying pathophysiology associated with increased CV risk in T1D. In the current review, we will provide a detailed overview of the current evidence for a role of HDL function as independent risk factor for the development of CVD in T1D.

1. T1D: introduction

Type 1 diabetes (T1D), is a chronic autoimmune metabolic disease characterized by deficiency in insulin secretion due to destruction of the pancreatic beta-cells leading to disturbed glucose metabolism [1–4]. T1D accounts for 7–12% of the total diabetes population and leads to long-term complications [5]. The inadequate supply of insulin in T1D results in elevated glucose concentrations or hyperglycemia, which is reflected by elevated hemoglobin A1c (HbA1c); it has been shown that 1% increase in HbA1c is associated with 37% higher risk of developing advanced diabetes microvascular complications such as diabetic neuropathy and retinopathy [6]. In addition to HbA1c, serum glycated albumin, produced by early and advanced glycation, has been considered as a predictor of macrovascular complications [7]. Premature cardiovascular disease (CVD) is one of the most frequent causes of death in T1D and its occurrence rate is 2–4 times higher than in the non-diabetic population [8,9]. Diabetic nephropathy (DN), a

Abbreviations: ABCA1, ATP-binding cassette transporter A1; Apo-AI, apolipoprotein AI; Apo, apolipoprotein; CE/TG, ratio of cholesteryl ester-to-triglyceride; CEC, cholesterol efflux capacity; CETP, cholesterylester transfer protein; CRF, chronic renal failure; CVD, cardiovascular disease; DN, diabetic nephropathy; ESRD, end-stage renal disease; FMD, flow-mediated dilation; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Hp, haptoglobin; IDL, intermediate-density lipoprotein; IMT, intima-media thickness; LCAT, lecithin cholesterol acyl transferase; LDL, low-density lipoprotein; Lp-PLA2, lipoprotein-phospholipase A2; MPO, myeloperoxidase; OxLDL, oxidized LDL; PL, phospholipid; PLTP, phospholipids transfer protein; PON1, paraoxonase 1; RCT, reverse cholesterol transport; ROS, reactive oxygen species; SAA, serum amyloid A; S1P, sphingosine-1-phosphate; SR-BI, scavenger receptor class B type I; T1D, tType 1 diabetes; TICE, transintestinal cholesterol excretion; T1D-GC, type 1 diabetes with good glycemic control; T1D-PC, type 1 diabetes with poor glycemic control; VLDL, very low-density lipoprotein.

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microvascular complication in T1D, leads to 20–50% probability of developing end-stage renal disease (ESRD) [10], a condition characterized by increased urinary albumin excretion and gradual decrease in glomerular filtration [11]. Furthermore, obesity, selective insulin resistance and lipotoxicity, reported as important aspects of end-organ damage in T1D, could explain the observed chronic inflammation in atherosclerosis and diabetic kidney disease [11,12].

Hyperglycemia in T1D may result in increased oxidative stress and induces a low-grade inflammatory response leading to diabetic complications [13], which may decrease significantly by insulin replacement therapies and meticulous glycemic control [5]. Although insulin treatment improves glucose metabolism in T1D [14], the diabetes-related disease burden increases with time for the development of chronic complications [11] associated with the long-term levels of HbA1c and diabetes duration in those patients with poor metabolic control [15].

2. Lipid abnormalities in type 1 diabetes

Type 1 diabetic patients exhibit impaired lipid profiles, which may be associated with the development of late diabetic complications [16]. In Table 1, a summary is given documenting plasma lipid levels in a large number of published studies. Increased HDL-C levels were observed in T1D patients without chronic renal failure (CRF) [17], whereas slightly elevated TG and lower HDL-C levels are found in T1D patients with CRF [11,18,19]. Macroalbuminuria was associated with elevated plasma TG and altered very low-density lipoprotein (VLDL)-HDL balance in patients with long-standing T1D [11]. Lower HDL_2-C concentrations have been associated with microalbuminuria in T1D and T1D patients with altered body weight and glycemic control [20,21]. Thus keeping circulating glucose levels close to the physiological range may have a positive impact on lipid metabolism [22–24], resulting in a significant reduction in serum TG levels, while HDL-C concentrations were markedly increased [25,26]. Nonetheless, it has been observed that despite the favorable lipid changes following adequate glucose control in T1D, it may be insufficient to normalize lipids in T1D patients with existing dyslipidemia [22]. Reduced HDL TG content has been reported in T1D subjects, making the particles more susceptible for the action of CETP [27]. Indeed, low CEs were found in small HDL3 from T1D patients [28], which could be linked to high CETP activity, a common feature in T1D [28]. To date, it has been established that HDL particles from T1D patient have low capacity to protect against lipid oxidation [15]. The exact impact of these changes on HDL functionality in T1D patients is still not fully understood.

3. Search strategy

In this review, all published articles up to September 3, 2017 were considered by searching in Scopus (http://www.scopus.com) and Medline (http://www.ncbi.nlm.nih.gov/pubmed) without any language restriction. The search terms included “Type 1 diabetes” OR “Type I diabetes” OR “insulin-dependent diabetes” OR “childhood diabetes” OR “autoimmune diabetes” AND “high-density lipoprotein functionality” OR “reverse cholesterol transport” OR “lipid transfer” OR “cholesterol efflux” OR “ATP-binding cassette transporter A1” OR ″ ATP-binding cassette transporter G1” OR “scavenger receptor class B, type I” OR “lecithin-cholesterol acyltransferase” OR “cholesteryl ester transfer protein” OR “Phospholipid transfer protein” OR “antioxidant function” OR “apo-AI” OR “anti-inflammatory function” OR “paraoxonase-1” OR “phospholipase A2” OR “myeloperoxidase” OR “sphingosine-1-phosphate” OR “serum amyloid A” in titles and abstracts. Finally, after reading the abstracts, we have chosen articles which were related to our subject. Then, we assessed in full text and excluded duplicate documents. Finally, 79 articles were eligible for the review.

4. HDL: biology, metabolism and relation to atherosclerotic cardiovascular disease

HDL particles are a heterogeneous class of plasma lipoproteins and vary in terms of size and composition. A number of HDL subclasses have been defined: large (HDL2b and HDL2a) and small (HDL3a, HDL3b, and HDL3c) particles [24], which differ in shape,

Table 1
Plasma lipid levels in T1D *versus* controls.

Triglycerides		HDL cholesterol		Mean age	Number
Control	Type I diabetes	Control	Type 1 diabetes	(DM1–control)	(DM1–control)
92.5 ± 24.6 mg/dl	85.6 ± 23.1 mg/dl	58.6 ± 18.9 mg/dl	54.3 ± 18.4 mg/dl	39.6 ± 14.0–45.8 ± 13.7	N = 12–6 [94]
102.7 ± 33.0 mg/dl	100.3 ± 46.0 mg/dl	51.6 ± 12.0 mg/dl	55.3 ± 12.0 mg/dl	28.8 ± 3.3	N = 20–20 [46]
0.86 ± 0.24 mmol/L	1.16 ± 0.77 mmol/L[a]	1.48 ± 0.41 mmol/L	1.62 ± 0.46 mmol/L	42.1 ± 15.9–43.07 ± 14.922	N = 70–83 [63]
0.96 ± 0.6 mmol/L	0.74 ± 0.3 mmol/L	1.62 ± 0.4 mmol/L	1.46 ± 0.4 mmol/L	29.0 ± 6.5	N = 10–10 [95]
1.11 [0.8–1.5] mmol/L	1.06 [0.8–1.4] mmol/L	1.7 (0.41) mmol/L	1.8 (0.46) mmol/L[a]	38 (0.3)–38 (0.3)	N = 195–194 [17]
0.94 ± 0.32 mmol/L	1.11 ± 0.76 mmol/L	1.60 ± 0.28 mmol/L	1.65 ± 0.44 mmol/L	40.9 ± 14.3–45.1 ± 15.6	N = 54–50 [28]
93 ± 34 mg/dl	81 ± 37 mg/dl	69 ± 16 mg/dl	71 ± 15 mg/dl	27.8 ± 5.6–30.8 ± 6	N = 21–21 [96]
0.68 [0.52–0.95] mmol/L	0.66 [0.52–0.4] mmol/L	1.23 ± 0.44 mmol/L	1.45 ± 0.33 mmol/L[a]	13.92 ± 5.32–12.86 ± 5.41	N = 109–97 [97]
0.81 ± 0.51 mmol/L	0.72 ± 0.32 mmol/L	1.23 ± 0.44 mmol/L	1.44 ± 0.34 mmol/L	14.0 ± 5.3–12.9 ± 5.4	N = 122–97 [22]
0.82 ± 0.03 mmol/L	0.67 ± 0.06 mmol/L	1.38 ± 0.02 mmol/L	1.65 ± 0.07 mmol/L	13.0 ± 0.5	N = 22–131 [26]
0.70 [0.51–0.86] mmol/L	0.74 [0.55–1.12] mmol/L	1.7 ± 0.4 mmol/L	1.7 ± 0.3 mmol/L	13.1 ± 3.6–13.2 ± 3.9	N = 30–30 [82]
115.9 ± 29.3 mg/dl[a]	84.7 ± 29.7 mg/dl	45.5 ± 8.5 mg/dl	46.1 ± 10.1 mg/dl	37.2 (6.9)–47.3 (9.2)	N = 10–14 [72]
1.1 (0.40) mmol/L	1.3 (0.83) mmol/L	1.5 (0.4) mmol/L	1.6 (0.53) mmol/L	32.6 (11.3)–42.4 (11.3)[a]	N = 20–23 [53]
1.0 ± 0.3 mmol/L	0.9 ± 0.5 mmol/L	1.3 (1.1–1.7) mmol/L	1.6 (1.3–1.8) mmol/L	42.5 ± 9.4–38.2 ± 10.3	N = 37–34 [55]
99 ± 16 mg/dl	92 ± 13 mg/dl	66 ± 5 mg/dl	57 ± 3 mg/dl	26 ± 2–28 ± 2	N = 13–12 [7]
120 ± 87.9 mg/dl	71.8 ± 18.83 mg/dl	44.4 ± 12.7 mg/dl	44.4 ± 6.64 mg/dl	33.6 ± 12.97–35.2 ± 13.19	N = 15–15 [5]
1.08 ± 0.33 mmol/L	1.18 ± 0.63 mmol/L	1.14 ± 0.08 mmol/L	1.14 ± 0.05 mmol/L	26.3 ± 6.5–26.5 ± 4.2	N = 10–10 [64]
1.31 (0.77) mmol/L	1.04 (0.39) mmol/L	1.41 (0.34) mmol/L	1.50 (0.41) mmol/L	35.8 (8.3)–39.4 (10.1)	N = 50–49 [85]
0.9 ± 0.1 mmol/L	0.9 ± 0.1 mmol/L	1.4 ± 0.1 mmol/L	2.0 ± 0.1 mmol/L	31.7 ± 1.9–30.3 ± 1.7	N = 24–20 [85]
0.98 (0.71–1.49) mmol/L	0.87 (0.68–1.12) mmol/L	1.31 (0.34) mmol/L	1.53 (0.36) mmol/L	40 (29–51)–34 (30–44)	N = 35–24 [27]
0.55 (0.10–1.76) mmol/L	0.62 (0.11–3.68) mmol/L	1.4 ± 0.3 mmol/L	1.5 ± 0.3 mmol/L	13.6 ± 2.6–13.3 ± 2.5	N = 79–61 [23]
1.0 (0.9–1.2) mmol/L	0.9 (0.6–1.3) mmol/L	1.3 (1.2–1.4) mmol/L	1.7 (1.4–2.0) mmol/L[a]	34.4 ± 6.3–31.1 ± 10.8	N = 80–24 [15]
2.5 (0.8–8.9) mmol/L	2.9 (0.8–13.7) mmol/L[a]	1.1 (0.1) mmol/L[a]	1.2 (0.1) mmol/L	55 (2)–58 (1)[a]	N = 23 (19)–40 (34) [98]

[a] Significant.