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Lipoprotein composition in patients with type 1 diabetes mellitus: Impact of lipases and adipokines

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ABSTRACT

Objective: High cardiovascular mortality in patients with type 1 diabetes (T1DM) is widely recognized. Paradoxically, these patients have been shown to have elevated HDL-C and reduced apoB-containing lipoproteins. The purpose of this investigation was to further characterize the lipoprotein composition in T1DM and to assess the role that lipases and adipokines may play in these differences.

Methods: T1DM patients (89) attending the Diabetes Clinic at the University of Miami and 42 healthy controls were recruited. Clinical characteristics, lipoprotein composition (by ultracentrifugation and HPLC), leptin, and adiponectin were measured in the full cohort, while a subgroup had LPL and hepatic lipase measured.

Results: Subjects were predominately Caucasian and Hispanic. HgbA1c's were above goal while their mean duration of diabetes was >20 years. LPL was 2-fold elevated in diabetic women versus controls (+107%{p = 0.001}) with no difference in men. Hepatic lipase was reduced 50% {p < 0.001} in women but increased 50% {p = 0.079} in men. Leptin was similar to controls in women but reduced in men (−60%{p < 0.001}). Adiponectin was elevated in both genders (men: +55%{p = 0.018}; women: +46%{p = 0.007}).

LDL-C was reduced in both diabetic men (−33%{p < 0.001}) and women (−24%{p < 0.001}) while HDL-C trended higher only in men (+13%{p = 0.064}). Both total apoB (men: −31%{p < 0.001}; women: −17%{p = 0.016}) and triglycerides (men: −49%{p < 0.001}; women: −31%{p = 0.011}) were reduced in both genders while total apoA-I was increased in both (men: +31%{p < 0.001}; women: +19%{p = 0.008}). Both men and women had increases in LpA-I (+66%{p < 0.001}; +40%{p = 0.001}) which accounted for essentially the entire increase in HDL mass. VLDL lipids (men: −53 → 70%; women: −31 → 57%) were lower as was apoB (particle number) in men (−51{p < 0.001}) with a similar trend in women (−35%{p = 0.066}). Cholesterol esters in the particle core were depleted in both genders relative to both apoB (men: −41%; women: −37%) and triglycerides (men: −38%; women: −34%) (all{p < 0.009}). There were similar differences in IDL.

HDL-L lipids (except triglycerides) (men: +45 → 74%; women: +49 → 77%{p < 0.006}), apoA-1 (men: +162%; women: +117%{p < 0.001}), and apoA-II (men: +64%{p = 0.008}; women: +55%{p = 0.014}) were higher in T1DM patients. These differences produced dramatic increases in LpA-I (men: +221%; women +139%{p < 0.001}) and total HDL-L mass (men: +85%; women: +78%{p < 0.001}). ApoM (men: +190%; women: +149%{p < 0.001}) was also dramatically increased. Conversely, HDL-D lipids were lower in both genders (−20% → 50%) while apoA-I was not different in either. ApoA-II was lower only in the diabetic women (−25%{p = 0.015}).

LPL activity correlated primarily with IDL(−), LDL(−), HDL-L(+), and HDL-D(−) only in the women. HL correlated weakly with VLDL(+), LDL(+), HDL-L(−), and HDL-D(+) in women but had much stronger correlations with VLDL(−), IDL(−), and HDL-L(+). Adiponectin correlated with VLDL(−), IDL(−), LDL(−), HDL-L(+), and HDL-D(−) in women but only HDL-L(+) and HDL-D(−) in men. Leptin correlated with very few parameters in women but did correlate weakly with several HDL-L(−) and HDL-M(−) parameters.

Conclusion: Lipoprotein composition and adipokine concentrations in both genders as well as lipase activities in the women would be expected to reduce the atherosclerotic risk in these patients with T1DM. These data suggest that there are functional lipoprotein abnormalities responsible for their CV risk that are not reflected in their plasma concentrations.

1. Introduction

High cardiovascular (CV) mortality in type 1 diabetes (T1DM) is widely recognized. In the United Kingdom prior to 2006, the hazard ratio for CV mortality in women was 11.6 while in men it was 5.8

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(Soedamah-Muthu et al., 2006). An 18-year, prospective, observational study in Finland showed very similar hazard ratios (women 13.3, men 3.6) which were also comparable to T2DM patients in the same study (Juutilainen, Lehto, Ronnemaa, Pyorala, & Laakso, 2008). They also demonstrated a substantially greater impact of poor glycemic control in T1DM than in T2DM. In a later UK study, the age-adjusted incidence rate had declined but was still substantial (women 3.5, men 3.4) and the rates of first cardiovascular events were similar (Livingstone et al., 2012).

Severity of atherosclerosis in T1DM as measured by carotid ultrasound has been correlated with LDL (low density lipoprotein) subfractions, LDL particle number, LDL cholesterol (LDL-C), apoB (Lyons et al., 2006), age, hypertension, smoking, retinopathy, high density lipoprotein cholesterol (HDL-C) (Distiller, Joffe, Melville, Welman, & Distiller, 2006), and adiponectin (Yazıcı et al., 2012). Progression of coronary calcification is positively correlated with non-HDL cholesterol and albumin excretion rate (AER) (Costacou, Edmundowicz, Prince, Conway, & Orchard, 2007). Ruppert, Roberts, Orchard, and Zgibor (2007) reported in a 10 year, prospective observational study in Pittsburgh, PA, that standard Framingham risk factors, AER, and HDL-C predicted MI, CV death, or Q-waves in men while in women, depression, HgbA1c, AER, LDL-C, non-HDL-C, waist to hip ratio (WHR), and glucose disposal rate were predictive. In a subsequent report on this population (Costacou, Evans, & Orchard, 2011), HDL-C and HDL_3 cholesterol were inversely correlated with cardiovascular events in both men and women. However, if HDL-C was >80 mg/dl in women, then events were increased. Makinen et al. (2008) also demonstrated that the metabolic syndrome (insulin resistance, abdominal obesity, high triglycerides, low HDL_2 cholesterol, and low adiponectin) was associated with increased mortality in over 4,000 T1DM men and women over 6.5 years. In a subsequent report, they added intermediate density lipoprotein (IDL) cholesterol as an important predictor (Niemi et al., 2009). In the EURODIAB study (Soedamah-Muthu et al., 2008), CV mortality was positively correlated with systolic blood pressure, triglycerides, waist-to-hip ratio, AER, hypertension, retinopathy, and autonomic neuropathy but negatively correlated with HDL-C in 2,787 patients over 7 years. In addition, Forsblom et al. (2011) surprisingly found that CVD and total mortality were positively correlated with adiponectin, even in patients without renal disease.

Nikkila and Hormila (1978) first reported that T1DM patients had higher HDL-C and lower very low density lipoprotein triglycerides (VLDL-TG) than subjects without diabetes and that these differences were associated with an increase in lipoprotein lipase (LPL) activity. Subsequently, Eckel et al. (1981) reported that apoA-I was also elevated in T1DM while Kahri, Groop, Viberti, Elliott, and Taskinen (1993) demonstrated increases in HDL_2, LpA-I (HDL containing only apoA-I), and LPL. There were no differences in hepatic lipase (HL) or cholesterol ester transfer protein (CETP) activities when it was measured in these studies.

Verges (2009) recently reviewed lipid disorders in T1DM. He noted that when T1DM is complicated by insulin resistance (high triglycerides, low HDL-C, and small, dense LDL), proteinuria (high LDL-C), or reduced kidney function typical lipoprotein changes were seen (high triglycerides, low HDL-C). In addition, HgbA1c is typically correlated positively with LDL-C and triglycerides as well as VLDL production. Therefore, in patients with optimal control, triglycerides and LDL-C were similar to controls or slightly reduced while HDL-C was normal or slightly increased. He suggested that these differences may be caused by reduced VLDL production and elevated LPL activity driven by the peripheral hyperinsulinemia typically seen in treated-T1DM. He also noted that there have been reports of both elevated HDL_2 and/or HDL_3 cholesterol as well as increased LpA-I in T1DM. Recently, Fukui and Hirano (2012) described a Japanese population of patients with T1DM (HgbA1c 7.4 ± 2.3%) with a similar lipoprotein composition. Their HDL-C, HDL_2 cholesterol, and HDL_2 apoA-I were elevated while LDL-C, total triglycerides, apoA-I, apoA-II, HDL_3 cholesterol, and HDL_3 apoA-I were not different than controls. Conversely, Feitosa, Feitosa-Filho, Freitas, Wajchenberg, and Maranhao (2013) reported lower LDL-C and more rapid LDL-C clearance in poorly controlled T1DM compared to control subjects.

Verges (2009) discussed the important role that glycation and oxidation may have on lipoproteins and the various enzymes and receptors that control lipoprotein metabolism. They explained that even though lipoprotein concentrations may appear to be in a beneficial range, their function may be impaired, leading to an adverse effect on atherogenesis. In addition, there are possible genetic causes for apparent dysfunction in T1DM patients. The LIPC-480C > T polymorphism of hepatic lipase Hokanson et al. (2002) occurs in about 25% of patients and reduces lipase activity leading to increases in HDL-C and HDL_2. However, they have more coronary calcification.

The purpose of this investigation was to first, perform an extensive evaluation of the structural composition of lipoproteins in patients with T1DM in order to determine if there were abnormalities that could explain their high cardiovascular risk despite beneficial levels of the typical parameters (i.e. LDL-C, HDL-C, triglycerides, apoA-I, and apoB). Second, assess the potential impact of lipases and adipokines on these lipoprotein parameters. Our hypothesis is that even though compositional lipoprotein differences are important in atherogenesis, functional lipoprotein abnormalities are the dominate factors in determining cardiovascular events in T1DM. Assessing the impact of lipases and adipokines is the first step to identifying possible functional abnormalities.

2. Materials and methods

2.1. Subjects

Patients with T1DM (127) attending the Diabetes Clinic at the Diabetes Research Institute/University of Miami Miller School of Medicine were recruited. Exclusion criteria included age <18 years, pregnancy, chronic kidney disease, a recent cardiovascular event or other systemic disease, or fibrate or niacin therapy. Healthy, non-diabetic subjects (103) were recruited as controls by advertisement. The subgroup of patients and controls reported in this report consented for measurement of post-heparin lipolytic activity (69 T1DM and 42 controls) and lipoprotein compositional analysis by ultracentrifugation (89 T1DM and 42 controls). BMI, medications, and duration of disease were assessed during the first study visit. The study was approved by the Human Subjects Research Office of the University of Miami and written consent was obtained from all individuals.

2.2. Clinical and biochemical measurements

Blood samples were obtained from all subjects after an overnight fast. HgbA1c, total cholesterol, triglycerides, free cholesterol, phospholipids, and apoB were assayed by standard laboratory assays. Total adiponectin and leptin levels were quantitated in duplicate by ELISA (Mercodia.Inc). Both the intra and interassay coefficients of variation were <5%. Lipoprotein and hepatic lipase activities were measured in post-heparin plasma (Shepard et al., 2000).

2.3. Lipoprotein Separation by Ultracentrifugation

Lipoproteins were isolated and analyzed as previously described (Hughes, Gaber, & Montgomery, 1991; Hughes, Moore, Neame, Medley, & Chung, 1988) using gradient ultracentrifugation and HPLC. Nine ml of plasma was centrifuged and collected. The fractions were pooled into VLDL, IDL, LDL, and three HDL subfractions designated L, M, and D (lowest to highest density). These correspond roughly to HDL_{2b}, HDL_{2a+3a}, and HDL_{3b+3c}, respectively. The major

protein in each of the HDL subfractions is apoA-I and the subfractions are subdivided based on their apoA-II to A-I ratio. HDL-M has the highest apoA-II to apoA-I ratio and a medium buoyant density (d = 1.11 to 1.16 mg/ml) while both HDL-L (least dense) and HDL-D (most dense) have substantially lower apoA-II to apoA-I ratios.

Aliquots of VLDL, IDL, and each HDL pool were delipidated with human insulin added as an internal standard and injected onto an HPLC column for analysis. The coefficients of variation (C.V.) for the apolipoprotein concentrations were: apoA-I (0.4), apoA-II (3.9), apoC-III (3.6), apoC-II (2.3), and apoC-I (5.4). LpA-I:A-II particles (HDL particles containing both apoA-I and apoA-II) in HDL-L and HDL-M have a molar A-II/A-I ratio of 3:4 while HDL-D has a ratio of 1:2. From these known ratios, the number of LpA-I (HDL containing apoA-I without apoA-II) particles was calculated in each subfraction. We have not determined a response factor for apoM relative to our internal standard (insulin) so it is reported as "Insulin Units" which assumes that it has the same absorbance per microgram as insulin.

2.4. Statistical analyses

Statistical analyses were performed using JMP (SAS Institute Inc. 2012. *JMP® 10*, Cary, NC: SAS Institute Inc.). The distribution of variables was assessed for normality and, where necessary, logarithmically transformed. Data are expressed as means ± SEM. Two-tailed Student t-tests were applied to assess differences. Pearson correlation coefficients were used to describe the association between continuous variables.

3. Results

3.1. Patient Characteristics

The study population was predominately Caucasian and Hispanic and both genders were well matched for age and BMI (Table 1). Twenty-seven percent of the diabetic women and 20% of the men had a BMI ≥ 30 while 18% of control women and none of the control men had a BMI ≥ 30. HgbA1c's were above goal and their duration of diabetes was 24.3 years (men) and 29.8 years (women). Only seven women and nine men had an HgbA1c < 7.0%. Eighteen percent of diabetic women and 5% of diabetic men had micro-albuminuria but none had an elevated serum creatinine. Forty percent of diabetic patients were on a statin at the time of this study but, when non-statin users were analyzed separately, lipoprotein differences were the same unless noted. LPL was 2-fold elevated in diabetic women compared to controls (+107%{p = 0.001}) while there was no difference in men. Hepatic lipase was reduced by 50% {p < 0.001} in the women while it was increased by 50% {p = 0.079} in diabetic men compared to controls. The hsCRP was not different in patients compared to controls. Leptin was similar to controls in the diabetic women but it was reduced in diabetic men (−60%{p < 0.001}). Adiponectin was elevated in both genders relative to non-diabetic controls (men: +55%{p = 0.018}; women: +46%{p = 0.007}). Diabetic women had higher LPL, leptin, and adiponectin but lower HL than diabetic men.

In women (combined controls and patients), BMI was positively correlated with hsCRP (r^2 = 0.288{p < 0.001}) and leptin (r^2 = 0.486{p < 0.001}) but negatively correlated with adiponectin (r^2 = 0.194{p = 0.002}). BMI was not correlated with the lipases. Leptin and hsCRP were positively correlated (r^2 = 0.079{p = 0.029}) but hsCRP was not correlated with adiponectin or the lipases. Leptin was not correlated with adiponectin or the lipases nor was adiponectin correlated with the lipases. The lipases were not correlated with each other.

In men, BMI was positively correlated with hsCRP (r^2 = 0.094{p = 0.013}) but neither were correlated with any of the other measured parameters. Leptin was negatively correlated with adiponectin (r^2 = 0.078{p = 0.025}) and LPL was positively correlated with HL (r^2 = 0.080{p = 0.046}) while the adipokines were not correlated with the lipases.

3.2. Total Plasma

LDL total cholesterol (LDL-C) was reduced in both diabetic men (−33%{p < 0.001}) and women (−24%{p < 0.001}) but HDL-C trended higher only in diabetic men (+13%{p = 0.064}) (Table 2). The LDL-C/HDL-C ratios (men: −43%{p < 0.001}; women: −32%{p = 0.006}) and triglycerides (TG) were reduced in both genders (men: −49%{p < 0.001}; women: −31%{p = 0.011}). ApoB was also reduced in both genders (men: −31%{p < 0.001}; women: −17%{p =0.016}) while apoA-I was increased in both (men: +31%{p < 0.001}; women: +19%{p = 0.008}). There were no differences in the apoC's in either gender but both had increased LpA-I (men: +66%{p < 0.001}; women: +40%{p = 0.001}). Diabetic women had higher total cholesterol, apoC-III, and LpA-I than diabetic men but a lower LDL/HDL ratio.

LDL-C in women was negatively correlated with LPL and adiponectin but positively correlated with HL such that the increase in LPL and adiponectin combined with the reduction in HL in the diabetic women accounted for almost 40% of the reduction in LDL-C seen in this group (Table 2). Adiponectin was the dominate factor. None of the measured parameters was correlated with LDL-C in the men. HDL-C in women was positively correlated with LPL and adiponectin which accounted for approximately 30% of the increase

Table 1
Demographics, Lipases, and Cytokines (mean + SEM).

	Women					Men				DM women vs. men	
	Controls	Diabetic	p-value	% Diff		Controls	Diabetic	p-value	% Diff	p-value	% Diff
Age (means)	45.0 ± 13.1	47.4 ± 13.7	ns	5%	Age (means)	43.5 ± 10.0	43.6 ± 12.5	ns	0%	ns	9%
(range)	28.9–61.8	20.9–71.5			(range)	30.2–62.5	18.4–64.2				
Number	22	45			Number	20	44				
BMI	25.8 ± 3.9	27.0 ± 5.9	ns	5%	BMI	25.5 ± 3.3	27.4 ± 3.7	0.052	7%	ns	−1%
Ethnicity (C/H/AA)*	7/14/1	23/18/4			Ethnicity (C/H/AA)*	7/12/1	21/19/4				
Statin use (%)	5	44			Statin use (%)	20	39				
DM duration (yrs)		29.8 ± 13.9			DM duration (yrs)		24.3 ± 13.6			ns	23%
HgbA1c (%)		8.1 ± 1.5			HgbA1c (%)		7.9 ± 1.2			ns	3%
LPL (umol FFA)	2.72 ± 1.59	5.62 ± 3.85	0.001	107%	LPL (umol FFA)	3.66 ± 1.75	3.70 ± 2.97	ns	1%	0.027	52%
HL (umol FFA)	3.99 ± 2.66	2.00 ± 1.37	<0.001	−50%	HL (umol FFA)	5.04 ± 2.67	7.57 ± 5.91	0.079	50%	<0.001	−74%
Cytokines:					Cytokines:						
hsCRP	2.17 ± 2.03	3.70 ± 3.75	0.079	71%	hsCRP	1.88 ± 2.15	2.66 ± 4.67	ns	41%	ns	39%
Leptin	24.15 ± 19.46	31.93 ± 20.8	ns	32%	Leptin	20.0 ± 17.2	10.3 ± 8.9	0.004	−49%	<0.001	210%
Adiponectin	11.21 ± 4.09	15.92 ± 7.88	0.011	42%	Adiponectin	8.0 ± 2.8	11.8 ± 7.5	0.034	48%	0.013	35%

* Caucasian/Hispanic/African-American.

Table 2
Total Plasma Lipids (Mean + SEM).

	Women				Correlations: all women				Men				Correlations: all men				DM women vs. men	
Total plasma:	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	Total plasma:	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	p-value	%Diff
Total cholesterol	5.10 ± 0.97	4.46 ± 0.72	0.004	−13%	–	−6.2	11.5	–	Total cholesterol	5.27 ± 0.96	3.93 ± 0.81	<0.001	−25%	–	–	–	–	0.001	13%
Triglyceride	1.27 ± 0.87	0.87 ± 0.40	0.011	−31%	–	−7.0	7.3	–	Triglyceride	1.61 ± 0.98	0.82 ± 0.33	<0.001	−49%	–	–	−12.3	7.5	ns	6%
LDL cholesterol	2.63 ± 0.72	1.99 ± 0.56	<0.001	−24%	−10.1	−18.4	10.2		LDL cholesterol	2.91 ± 0.71	1.96 ± 0.72	<0.001	−33%	–	–	–	–	ns	2%
HDL cholesterol	1.57 ± 0.45	1.77 ± 0.49	ns*	13%	13.3	16.2	–	–	HDL cholesterol	1.15 ± 0.31	1.30 ± 0.28	0.064*	13%	–	13.6	–	−16.5	<0.001	36%
LDL/HDL chol	2.07 ± 1.11	1.40 ± 0.78	0.006	−32%	−6.4	−18.8	8.5	–	LDL/HDL chol	3.01 ± 1.07	1.72 ± 0.68	<0.001	−43%	–	−8.3	–	–	0.049	−19%
apoB	1.44 ± 0.45	1.20 ± 0.37	0.016	−17%	–	−16.5	8.5	–	apoB	1.65 ± 0.38	1.14 ± 0.31	<0.001	−31%	–	–	–	–	ns	5%
apoA-I	71.4 ± 13.2	85.2 ± 21.9	0.008	19%	18.0	–	–	–	apoA-I	59.9 ± 10.7	78.2 ± 22.9	0.001	31%	–	–	–	–	ns	9%
apoA-II	24.9 ± 5.9	25.4 ± 7.8	ns	2%	–	–	–	–	apoA-II	24.4 ± 4.9	26.9 ± 10.8	ns	10%	–	–	–	–	ns	−6%
apoC-III	18.4 ± 9.0	16.8 ± 5.1	ns	−9%	–	–	–	–	apoC-III	16.8 ± 8.1	14.1 ± 5.0	ns	−16%	–	–	–	–	0.015	19%
apoC-II	4.73 ± 2.69	4.52 ± 2.11	ns	−4%	–	–	12.8	–	apoC-II	5.40 ± 3.50	4.55 ± 1.86	ns	−16%	–	–	–	–	ns	−1%
apoC-I	13.0 ± 3.5	13.5 ± 4.3	ns	4%	–	–	–	–	apoC-I	12.1 ± 4.1	12.9 ± 4.5	ns	7%	–	–	–	–	ns	5%
LpA-I	34.8 ± 13.6	48.7 ± 17.4	0.001	40%	23.1	14.1	–	–	LpA-I	23.4 ± 10.3	38.9 ± 14.0	<0.001	66%	–	9.2	–	–	0.004	25%
(Lipids: mmol/l; apolipoproteins: nmol/l)			*p < 0.05 in non-statin users		(r2 x 100)				(lipids: mmol/l; apolipoproteins: nmol/l)			*p < 0.05 in non-statin users		(r2 × 100)					

in diabetic women. HDL-C in men was positively correlated with adiponectin but negatively correlated with leptin (~30% impact).

The impact of glucose control on lipoprotein composition was assessed by calculating correlations with HgbA1c as well as by dividing each gender at the median (7.7%) and calculating the differences by t-test. Within diabetic women, total cholesterol, free cholesterol, apoC-II, and LDL-C/HDL-C were positively correlated with HgbA1c at $p < 0.05$ ($r = 0.377$ to 0.404) while triglycerides, cholesterol esters, apoB, and apoB/apoA-I were positively correlated at $p < 0.01$ ($r = 0.416$ to 0.465). Total apoA-II was higher (16%, $p = 0.025$) while LpA-I was lower (−26%, $p = 0.046$) in the women with higher versus lower HgbA1c. Therefore, hyperglycemia reduced the differences between diabetic women and controls. There were no correlations or differences in the diabetic men between HgbA1c and the total plasma lipoprotein parameters.

3.3. VLDL

All VLDL lipids (Table 3) were reduced in both diabetic genders but reductions were more substantial in men (men: −53 → 70%; women: −31 → 57%) with cholesterol esters (CE) showing the largest reductions in both. VLDL apoB (and particle number) was reduced in men with a trend toward a reduction in women (men: −51%{$p < 0.001$}; women: −35%{$p = 0.066$}). There were also slightly greater reductions in the apoC's of men than women. The particle core was depleted of CE in both genders relative to both apoB (men: −41%; women: −37%) and triglycerides (men: −38%; women: −34%){$p < 0.009$}. The TG/apoB ratios were not different (data not shown). The particle surface lipid composition (free cholesterol (FC) to phospholipid (PL) ratios) and particle volume were not different from controls in either diabetic group. Total VLDL mass was reduced 56% in diabetic men {$p < 0.001$} and 39% in diabetic women {$p = 0.02$}. Therefore, both men and women had substantially fewer VLDL particles and these particles were depleted of cholesterol esters. However, their average particle volume was not different. There were no VLDL compositional differences between diabetic women and men.

In the women, VLDL lipids and apolipoproteins were only weakly correlated with adiponectin (neg) and HL (pos) while the men were more strongly correlated with HL (neg{$r^2 \times 100 \sim 13\%$}) but also weakly correlated with leptin (pos). The women had stronger correlations between VLDL composition (CE/apoB, CE/TG, and FC/PL) and LPL (neg{$r^2 \times 100 \sim 20\%$}).

Within diabetic women, CE, apoB, and apoC-I were positively correlated with HgbA1c at $p < 0.05$ ($r = 0.325$ to 0.360) while TC, FC, PL, TG, apoC-III, apoC-II, and total mass were positively correlated at $p < 0.01$ ($r = 0.415$ to 0.500). The CE/apoB was 33% higher ($p = 0.033$) in the women with higher versus lower HgbA1c. Therefore, hyperglycemia reduced the differences between diabetic women and controls. There were no correlations or differences in diabetic men between HgbA1c and VLDL parameters.

3.4. IDL

Similar to VLDL, all IDL lipids were reduced in both diabetic genders with reductions in men of greater magnitude (−40 → 60% versus −23 → 42%) (Table 4). IDL apoB was also reduced 37% {$p < 0.001$} in men but was not significantly reduced in women (−18%{ns}). However, if statin-users were excluded than IDL apoB was significantly reduced in women also. Both genders had significant reductions in IDL apoC-II (men: −43%{$p = 0.023$}; women: −44%{$p = 0.040$}) but IDL apoC-III was only reduced in men (−44%{$p = 0.025$}). Both genders had substantial reductions in the CE/apoB ratios (men: −41%{$p < 0.001$}; women −29%{$p < 0.001$}) but men also had substantial reductions in the CE/TG ratio (−32%{$p = 0.005$}). Women had an increase in the FC/PL ratio on their IDL surface

Table 3
VLDL Composition (Mean + SEM).

	Women				Correlations: all women				Men					Correlations: all men				DM women vs. men	
VLDL:	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	VLDL:	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	p-value	%Diff
Total cholesterol	0.380 ± 0.378	0.220 ± 0.157	0.017	−42%	–	−6.1	7.0	–	Total cholesterol	0.575 ± 0.418	0.233 ± 0.133	<0.001	−59%	–	–	−12.6	6.4	ns	−6%
Free cholesterol	0.258 ± 0.215	0.177 ± 0.086	0.030	−31%	–	–	–	–	Free cholesterol	0.361 ± 0.244	0.171 ± 0.080	<0.001	−53%	–	–	−12.1	6.4	ns	4%
Phospholipids	0.297 ± 0.252	0.181 ± 0.114	0.012	−39%	–	−5.6	8.4	–	Phospholipids	0.385 ± 0.268	0.175 ± 0.089	<0.001	−55%	–	–	−13.0	6.6	ns	3%
Triglycerides	0.755 ± 0.696	0.458 ± 0.304	0.017	−39%	–	–	9.0	–	Triglycerides	1.026 ± 0.806	0.440 ± 0.239	<0.001	−57%	–	–	−10.3	7.5	ns	4%
Cholesterol ester	0.174 ± 0.225	0.074 ± 0.098	0.014	−57%	–	−7.9	6.8	–	Cholesterol ester	0.293 ± 0.262	0.088 ± 0.083	<0.001	−70%	–	–	−12.0	–	ns	−16%
ApoB	0.102 ± 0.097	0.066 ± 0.058	0.066	−35%	–	−6.2	7.6	–	ApoB	0.140 ± 0.098	0.069 ± 0.042	<0.001	−51%	–	–	−16.5	–	ns	−4%
ApoC-III	6.02 ± 8.33	2.94 ± 3.01	0.030	−51%	–	–	8.0	–	ApoC-III	6.75 ± 7.63	2.67 ± 2.25	0.002	−60%	–	–	–	–	ns	10%
ApoC-II	2.17 ± 2.46	1.03 ± 1.11	0.011	−53%	–	−8.6	13.5	–	ApoC-II	2.80 ± 3.09	1.08 ± 0.79	0.001	−62%	–	–	–	–	ns	−4%
ApoC-I	2.31 ± 1.92	1.76 ± 1.58	ns	−24%	–	−7.6	6.4	–	ApoC-I	3.47 ± 3.35	1.63 ± 0.90	0.001	−53%	–	–	−8.4	–	ns	8%
Chol ester/apoB	1463 ± 530	925 ± 602	<0.001	−37%	−18.4	−5.9	7.2	–	Chol ester/apoB	1976 ± 671	1164 ± 823	<0.001	−41%	–	–	−9.8	7.9	ns	−21%
Chol ester/Trig	0.193 ± 0.077	0.127 ± 0.101	0.009	−34%	−22.9	−9.2	–	–	Chol ester/Trig	0.294 ± 0.121	0.181 ± 0.134	0.002	−38%	–	–	−18.0	–	0.036	−30%
F Chol/Phospholipid	0.896 ± 0.185	1.141 ± 0.817	ns*	27%	−17.7	−7.2	10.3	–	F Chol/Phospholipid	0.946 ± 0.110	1.000 ± 0.135	ns	6%	–	−6.0	−8.5	–	ns	14%
Total mass	111 ± 102	68 ± 45	0.02	−39%	–	–	–	–	Total mass	153 ± 115	67 ± 35	<0.001	−56%	–	–	–	–	ns	1%
Volume/apoB	46,216 ± 35,233	61,943 ± 74,697	ns	34%	–	–	–	–	Volume/apoB	37,657 ± 6,668	39,296 ± 19,035	ns	4%	–	–	–	–	0.057	58%

(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoB) (r2 × 100)

(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoB) (r2 × 100)

*p < 0.05 in non-statin users

Table 4
IDL Composition (Mean + SEM).

	Women				Correlations: all women				Men					Correlations: all men				DM women vs. men	
IDL:	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	IDL:	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	p-value	%Diff
Total cholesterol	0.213 ± 0.121	0.145 ± 0.109	0.024	−32%	−9.9	−10.0	–	–	Total cholesterol	0.322 ± 0.136	0.159 ± 0.095	<0.001	−51%	–	–	−17.3	–	ns	−9%
Free cholesterol	0.111 ± 0.047	0.085 ± 0.051	0.046	−23%	−9.7	−7.5	–	–	Free cholesterol	0.153 ± 0.055	0.092 ± 0.043	<0.001	−40%	–	–	−17.7	–	ns	−8%
Phospholipids	0.128 ± 0.059	0.085 ± 0.054	0.004	−34%	−13.5	−9.5	–	–	Phospholipids	0.160 ± 0.060	0.091 ± 0.042	<0.001	−43%	–	–	−18.6	8.3	ns	−7%
Triglycerides	0.172 ± 0.108	0.100 ± 0.064	<0.001	−42%	−9.5	−7.8	7.8	–	Triglycerides	0.212 ± 0.099	0.110 ± 0.052	<0.001	−48%	–	–	−16.1	7.3	ns	−9%
Cholesterol ester	0.140 ± 0.102	0.084 ± 0.086	0.020	−40%	−9.5	−9.9	–	–	Cholesterol ester	0.231 ± 0.119	0.092 ± 0.078	<0.001	−60%	–	–	−15.2	–	ns	−9%
ApoB	0.083 ± 0.037	0.068 ± 0.048	ns*	−18%	−11.4	−6.7	–	–	ApoB	0.111 ± 0.041	0.070 ± 0.040	<0.001	−37%	–	–	−15.7	–	ns	−3%
ApoC-III	0.744 ± 0.807	0.580 ± 0.548	ns	−22%	−10.3	–	–	–	ApoC-III	1.051 ± 1.127	0.593 ± 0.464	0.025	−44%	–	–	−8.2	–	ns	−2%
ApoC-II	0.254 ± 0.272	0.142 ± 0.167	0.040	−44%	−10.4	−8.2	7.9	–	ApoC-II	0.335 ± 0.336	0.192 ± 0.154	0.023	−43%	–	–	–	–	ns	−26%
ApoC-I	0.324 ± 0.227	0.305 ± 0.257	ns	−6%	−9.1	–	–	–	ApoC-I	0.456 ± 0.373	0.357 ± 0.186	ns	−22%	–	–	−14.6	–	ns	−15%
Chol ester/apoB	1524 ± 495	1078 ± 455	<0.001	−29%	−8.1	−6.4	9.3	–	Chol ester/apoB	2006 ± 479	1174 ± 509	<0.001	−41%	–	−7.0	−17.2	–	ns	−8%
Chol ester/Trig	0.787 ± 0.284	0.689 ± 0.389	ns	−12%	−11.1	–	–	7.4	Chol ester/Trig	1.121 ± 0.439	0.760 ± 0.464	0.005	−32%	–	–	–	–	ns	−9%
F Chol/Phospholipid	0.897 ± 0.175	1.055 ± 0.217	0.004	18%	17.1	8.3	–	–	F Chol/Phospholipid	0.961 ± 0.118	1.020 ± 0.139	ns	6%	–	7.8	–	–	ns	3%
Total mass	39.1 ± 21.3	25.9 ± 16.9	0.008	−34%	–	6.9	–	–	Total mass	51.7 ± 20.6	27.8 ± 13.8	<0.001	−46%	–	–	−11.7	–	ns	−7%
Volume/apoB	16,220 ± 2,380	14,422 ± 7,198	ns*	−11%	6.7	10.7	−8.6	5.9	Volume/apoB	16,932 ± 3,235	14,970 ± 3,519	0.039	−12%	–	–	–	–	ns	−4%

(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoB) (r2 × 100)

(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoB) (r2 × 100)

*p < 0.05 in non-statin users

Table 5
LDL Composition (Mean + SEM).

LDL:	Women				Correlations: all women				LDL:	Men				Correlations: all men				DM women vs. men	
	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin		Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	p-value	%Diff
Total cholesterol	2.63 ± 0.72	1.99 ± 0.56	<0.001	−24%	−10.1	−18.4	10.2	–	Total cholesterol	2.91 ± 0.71	1.96 ± 0.72	<0.001	−33%	–	–	–	–	ns	2%
Free cholesterol	0.863 ± 0.185	0.720 ± 0.172	0.003	−17%	−7.5	−17.1	–	–	Free cholesterol	0.940 ± 0.215	0.716 ± 0.248	<0.001	−24%	–	–	–	–	ns	1%
Phospholipids	0.913 ± 0.233	0.746 ± 0.187	0.003	−18%	−7.5	−17.9	–	–	Phospholipids	0.991 ± 0.218	0.726 ± 0.236	<0.001	−27%	–	–	–	–	ns	3%
Triglycerides	0.208 ± 0.077	0.189 ± 0.053	ns	−9%	–	−9.0	–	–	Triglycerides	0.208 ± 0.077	0.169 ± 0.046	<0.001	−19%	–	–	−11.9	–	0.071	12%
Cholesterol ester	2.43 ± 0.75	1.75 ± 0.56	<0.001	−28%	−10.7	−18.0	11.5	–	Cholesterol ester	2.70 ± 0.69	1.71 ± 0.68	<0.001	−37%	–	–	–	–	ns	2%
ApoB	1.230 ± 0.350	1.036 ± 0.285	0.027	−16%	–	−17.5	–	–	ApoB	1.386 ± 0.303	0.993 ± 0.303	<0.001	−28%	–	–	–	–	ns	4%
Chol ester/apoB	1985 ± 100	1676 ± 171	<0.001	−16%	−25.5	−6.1	19.0	–	Chol ester/apoB	1935 ± 172	1675 ± 228	<0.001	−13%	–	–	–	–	ns	0%
Chol ester/Trig	12.2 ± 3.3	9.5 ± 2.5	<0.001	−22%	–	–	14.0	–	Chol ester/Trig	11.8 ± 3.1	10.2 ± 3.4	0.070	−14%	–	–	–	–	ns	−7%
F Chol/Phosphol	0.955 ± 0.067	0.969 ± 0.062	ns	1%	–	–	–	–	F Chol/Phosphol	0.949 ± 0.053	0.981 ± 0.083	ns	3%	–	–	–	–	ns	−1%
Total mass	281 ± 78	225 ± 60	0.002	−20%	−8.2	−18.4	7.6	–	Total mass	312 ± 70	218 ± 71	<0.001	−30%	–	–	–	–	ns	3%
Volume/apoB	8,881 ± 267	8,193 ± 457	<0.001	−8%	−20.6	–	9.8	–	Volume/apoB	8,638 ± 468	8,209 ± 520	0.003	−5%	–	–	–	–	ns	0%
(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoB)					(r2 × 100)				(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoB)					(r2 × 100)					

(+18%{p = 0.004}). Both genders showed substantial reductions in IDL total mass (men: −46%{p < 0.001}; women: −34%{p = 0.008}) but their average IDL volumes were marginally smaller. Therefore, both diabetic men and women had substantially less IDL mass primarily by reducing particle numbers with only a marginal reduction in particle size. Both genders had less CE/particle in the IDL core while women had more FC molecules relative to PL molecules in their IDL surface lipid. There were no differences in IDL lipoprotein parameters between diabetic men and women.

Unlike VLDL, IDL lipids and apolipoproteins correlated with LPL {$r^2 \times 100$ ~ 10%} rather than HL in the women. However, adiponectin still played a significant role in the lipoprotein differences such that ~20% of the diabetic effect may be mediated by these 2 parameters. HL was again the dominate, measured factor in men but it accounted for <20% of the diabetic effect.

Within diabetic women, TC, FC, PL, CE, apoB, apoC-III, and total mass were positively correlated with HgbA1c at p < 0.05 (r = 0.327 to 0.400) while TG and apoC-II were positively correlated with HgbA1c at p < 0.01 (r = 0.445 and 0.467). There were no differences in IDL parameters in the women with lower versus higher HgbA1c. There were no correlations in diabetic men between HgbA1c and IDL parameters. However, TC (+39%, p = 0.026), PL (+30%, p = 0.042), CE (+54%, p = 0.018), CE/TG (+37%, p = 0.050), apoB (+38%, p = 0.032), and total mass (+32%, p = 0.032) were higher in the men with higher HgbA1c. Therefore, hyperglycemia reduced the differences between both diabetic women and men versus controls.

3.5. LDL

All LDL lipids (except TG), apoB, and total mass (men: ~30%{p < 0.001}; women: ~20%{p = 0.027}) were reduced in both genders with men showing ~10% greater reduction in all parameters (men all{p < 0.001}) (Table 5). Both genders showed similar reductions in their CE/apoB ratios (men −13%; women −16%{p < 0.001}). However, women also had a 22% reduction {p =0.001} in their core CE/TG ratio while men had only a 14% reduction {p = 0.070}. Neither gender had a difference in their surface FC/PL ratios. Both genders had reductions in their LDL volume (men: −5%{p = 0.003}; women: −8%{p < 0.001}). Therefore, both genders had fewer LDL particles and the particles were smaller. They also had less CE/particle with women having a TG-enriched core. Almost all LDL parameters were higher in men than women in the control group while they were almost identical in diabetic men and women, similar to their VLDL and IDL.

LPL, HL, and adiponectin correlated with the changes in diabetic women with adiponectin usually playing the dominate role. These three parameters accounted for approximately 40% of the difference in LDL cholesterol with adiponectin accounting for about half of the diabetic effect. None of the measured parameters played a significant role in men.

Within diabetic women, FC and apoB were positively correlated with HgbA1c at p < 0.01 (r = 0.489 and 0.491) while TC, PL, CE, and total mass were positively correlated with HgbA1c at p < 0.001 (r = 0.517 to 0.525). PL (+16%, p = 0.033), CE (+19%, p = 0.046), and total mass (+16%, p = 0.046) were higher in the women with higher versus lower HgbA1c. Therefore, hyperglycemia reduced the differences between diabetic women and controls. There were no correlations or differences in diabetic men between HgbA1c and LDL parameters.

3.6. HDL-L

HDL-L lipids (except TG) were increased in both diabetic men (45 → 74%{p < 0.006}) and women (49 → 77%{p < 0.006}) (Table 6). Both genders also had a substantial increase in HDL-L apoA-1 (men: +162%; women +117%{p < 0.001}) but smaller and similar increases

Table 6
HDL-L Composition (Mean + SEM).

	Women				Correlations: all women					Men				Correlations: all men				DM women vs. men	
HDL-L	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	HDL-L	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	p-value	%Diff
Total cholesterol	0.547 ± 0.310	0.853 ± 0.416	0.003	56%	27.1	24.5	–	–	Total cholesterol	0.312 ± 0.125	0.475 ± 0.221	0.003	52%	–	21.9	14.1	−13.6	<0.001	80%
Free cholesterol	0.172 ± 0.104	0.293 ± 0.150	0.001	70%	32.0	24.7	–	–	Free cholesterol	0.098 ± 0.036	0.165 ± 0.089	0.002	68%	–	19.4	9.9	−7.4	<0.001	78%
Phospholipids	0.388 ± 0.205	0.653 ± 0.314	<0.001	68%	29.0	22.8	−6.8	–	Phospholipids	0.211 ± 0.092	0.368 ± 0.206	0.002	74%	–	16.1	10.1	–	<0.001	77%
Triglycerides	0.040 ± 0.020	0.053 ± 0.026	0.053*	33%	–	–	−9.2	–	Triglycerides	0.034 ± 0.013	0.035 ± 0.022	ns	3%	–	7.5	–	–	<0.001	51%
Cholesterol ester	0.514 ± 0.284	0.767 ± 0.369	0.006	49%	24.1	23.9	–	–	Cholesterol ester	0.294 ± 0.123	0.426 ± 0.188	0.006	45%	–	21.9	16.3	−17.4	<0.001	80%
ApoA-I	10.5 ± 6.4	22.8 ± 12.8	<0.001	117%	39.1	20.0	−8.3	–	ApoA-I	5.0 ± 2.8	13.1 ± 8.2	<0.001	162%	–	20.2	10.3	–	<0.001	74%
ApoA-II	2.02 ± 0.93	3.14 ± 1.98	0.014	55%	12.1	–	–	–	ApoA-II	1.40 ± 0.60	2.30 ± 1.41	0.008	64%	–	11.1	14.7	–	0.024	37%
ApoC-III	3.69 ± 1.58	5.61 ± 2.27	<0.001	52%	17.6	9.0	−7.3	–	ApoC-III	2.21 ± 1.10	3.39 ± 1.62	0.004	53%	–	12.0	–	−9.3	<0.001	65%
ApoC-II	0.653 ± 0.380	1.021 ± 0.537	0.005	56%	14.5	14.2	–	–	ApoC-II	0.395 ± 0.201	0.726 ± 0.358	<0.001	84%	–	–	9.8	−10.9	0.003	41%
ApoC-I	2.71 ± 1.50	4.35 ± 2.20	0.002	61%	29.5	16.9	–	–	ApoC-I	1.49 ± 0.60	2.84 ± 1.52	<0.001	91%	–	23.4	9.1	−6.2	<0.001	53%
ApoM**	0.124 ± 0.107	0.308 ± 0.220	<0.001	149%	32.6	19.0	–	–	ApoM**	0.055 ± 0.028	0.160 ± 0.107	<0.001	190%	–	10.6	11.2	−7.5	<0.001	93%
LpA-I	7.8 ± 6.0	18.6 ± 11.5	<0.001	139%	39.0	21.5	−7.7	–	LpA-I	3.1 ± 2.6	10.0 ± 6.9	<0.001	221%	–	20.1	8.6	−7.6	<0.001	86%
apoA-II/apoA-I	0.236 ± 0.130	0.157 ± 0.098	0.007	−33%	–	17.1	–	–	apoA-II/apoA-I	0.329 ± 0.144	0.203 ± 0.105	<0.001	−38%	–	−7.8	–	10.4	0.038	−23%
apoC-III/apoA-I	0.413 ± 0.164	0.280 ± 0.112	<0.001	−32%	−9.5	−12.3	16.3	–	apoC-III/apoA-I	0.490 ± 0.196	0.305 ± 0.142	<0.001	−38%	–	−7.8	–	–	ns	−8%
apoC-II/apoC-III	0.174 ± 0.069	0.181 ± 0.052	ns	4%	–	–	–	–	apoC-II/apoC-III	0.187 ± 0.054	0.228 ± 0.091	0.068	22%	–	–	–	–	0.004	−21%
Chol ester/apoA-I	54.0 ± 17.1	37.4 ± 13.3	<0.001	−31%	−11.2	–	21.4	−7.4	Chol ester/apoA-I	66.8 ± 24.6	38.0 ± 15.9	<0.001	−43%	–	–	–	–	ns	−2%
Chol ester/Trig	13.1 ± 4.4	15.8 ± 6.1	0.072	21%	17.2	14.3	–	–	Chol ester/Trig	9.29 ± 3.5	13.5 ± 5.1	<0.001	45%	–	–	27.8	−16.8	0.060	17%
F Chol/Phosphol	0.438 ± 0.063	0.448 ± 0.062	ns	2%	–	–	–	–	F Chol/Phosphol	0.482 ± 0.095	0.451 ± 0.064	ns	−6%	–	–	–	–	ns	−1%
Total mass	98 ± 52	174 ± 84	<0.001	78%	32.9	21.9	−7.0	–	Total mass	54 ± 23	100 ± 54	<0.001	85%	–	20.3	10.9	−7.1	<0.001	74%
Volume/apoA-I	357 ± 72	282 ± 51	<0.001	−21%	−13.8	−6.8	19.6	−6.6	Volume/apoA-I	426 ± 106	288 ± 65	<0.001	−32%	–	−6.3	–	–	ns	−2%

(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoA-I) (r2 × 100)
**Insulin units (see Methods)
*p < 0.05 in non-statin users

(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoA-I) (r2 × 100)
**Insulin units (see Methods)

in apoA-II (men: +64%{p = 0.008}; women: +55%{p = 0.014}). Therefore, their apoA-II to apoA-I ratios were reduced (men: −38%; women: −33%) leading to dramatic increases in LpA-I (men: +221%; women +139%{p < 0.001}). There were also dramatic increases in apoM (men: +190%; women: +149%{p < 0.001}). The total HDL-L mass was increased by 85% in diabetic men and 78% in women {p < 0.001}. The lipid core was more CE enriched in men (+45%{p < 0.001}) with a trend in women (+21%{p = 0.072}) but both had reductions in their CE/apoA-I ratios (men: −43%; women −31%{p < 0.001}). Their surface lipid composition (FC/PL) was similar to controls. Unlike apoB-containing lipoproteins in which there is only one apoB molecule per particle, HDL particles can have a range of apoA-I molecules per particle. This analysis suggests that the additional LpA-I particles were carrying fewer CE and apoC molecules per apoA-I molecule. As would be expected, the diabetic women had much higher concentrations of all HDL-L components than the diabetic men but most of their compositional measurements (ratios) were similar.

LPL and adiponectin played dominate roles in HDL-L differences in women with HL playing a smaller role. However, unlike the apoB-containing lipoproteins, these parameters frequently accounted for >50% of the differences seen in this subfraction, with LPL usually having the dominate effect. However, in the men, LPL was not correlated with any of the HDL-L components while adiponectin and HL had the strongest correlation (adiponectin having the greatest impact). For the first time, Leptin appeared to have a significant impact on diabetic differences in HDL-L components, particularly on cholesterol differences. These parameters accounted for approximately 30% → 50% of the differences seen in diabetic men.

Within diabetic women, PL/apoA-I and CE/apoA-I were positively correlated with HgbA1c (r = 0.355 and 0.342) while FC, apoA-I, apoC-I, apoM, LpA-I, and total mass were negatively correlated with HgbA1c at p < 0.05 (r = 0.317 to 0.366). ApoC-III/apoA-I was positively correlated with HgbA1c at p < 0.001 (r = 0.512). TG (−34%, p = 0.051), apoC-I (−41%, p = 0.035), apoM (−64%, p =0.051), and LpA-I (−55%, p = 0.033) were lower in the women with higher HgbA1c while apoA-II/apoA-I was higher (+35%, p = 0.038). Therefore, hyperglycemia reduced the differences between diabetic women and controls. Within diabetic men, FC/apoA-I (r = 0.374, p < 0.05) and PL/apoA-I (r = 0.523, p < 0.01) were positively correlated with HgbA1c while PL/apoA-I was 14% higher in the men with higher HgbA1c (p = 0.024).

3.7. HDL-M

There were fewer HDL-M differences in diabetic patients (Table 7). TG was reduced in both genders (men: −35%{p < 0.005}; women: −26%{p = 0.005}) but apoM was increased (men: +61%; women: +62%{p < 0.001}). Men also had increases in apoA-I (+30%{p = 0.005}), apoC-II (+34%{p = 0.034}), apoC-I (+29%{p = 0.040}), and total mass (+16%{p = 0.037}) without an increase in apoA-II so they had a 56% increase in LpA-I {p < 0.001}. Both genders had CE enrichment of their core lipid (men: +65%{p < 0.001}; women: +29%{p = 0.046}) but no difference in surface lipid composition (FC/PL). They also both had increases in their apoC-II/apoC-III ratios but a reduction in their apoC-III/apoA-I ratios. Diabetic women had higher concentrations of all HDL-M lipids than men except for TG but their apolipoprotein concentrations and total mass were similar.

Of the measured parameters, LPL had the greatest impact on HDL-M TG in women while adiponectin had a smaller effect. Conversely, in men, HL had the greatest impact while leptin played a smaller role (combined effect approximately 35% in both cases). Similar, but less powerful effects were seen on apoM (combined effects approximately 20%). None of these parameters were correlated with the differences in apoA-I or LpA-I.

Within the diabetic women, apoA-II (r = 0.397, p < 0.05) and apoA-II/apoA-I (r = 0.424, p < 0.01) were positively correlated with HgbA1c while apoM/apoA-I (r = −0.324, p < 0.05) was negatively correlated. ApoA-II (+16%, p = 0.051) and apoA-II/apoA-I (+16%, p = 0.034) were higher in the women with higher HgbA1c while apoC-II/apoC-III (−26%, p = 0.027) and apoM/apoA-I (−13%, p = 0.027) were lower. The control women's apoA-II was between the values in the lower versus higher HgbA1c. There were no correlations or differences in diabetic men between HgbA1c and HDL-M parameters.

3.8. HDL-D

Both genders had significant and similar reductions in HDL-D total cholesterol, PL, TG, and CE (−20% → 50%) (Table 8). However, apoA-I was not different in either gender while apoA-II was lower in diabetic women (−25%{p = 0.015}). LpA-I trended higher only in men (+24%{p = 0.055}) while women had a small reduction in total mass (−13%{p = 0.050}). Diabetic women had lower concentrations of HDL-D apoA-II than diabetic men.

LPL, HL, and adiponectin correlated with the HDL-D lipid and total mass differences in women, combining for >30% effect, whereas only HL and adiponectin were factors in men, accounting for <20% of the differences seen.

Within diabetic women, FC, CE, apoA-I, and apoA-II/apoA-I (r = 0.323 to 0.388) were positively correlated with HgbA1c at p < 0.05 while TC, PL, apoA-II, and total mass (r = 0.422 to 0.477) were positively correlated at p < 0.01. TC (+21%, p = 0.021), FC (+25%, p = 0.007), PL (+24%, p = 0.025), apoA-II (+29%, p = 0.012), apoA-II/apoA-I (+21, p = 0.023), and total mass (+16%, p = 0.046) were higher in the patients with higher HgbA1c. Therefore, hyperglycemia reduced the differences between diabetic women and controls. Within the diabetic men, only the FC/apoA-I was negatively correlated with HgbA1c (r = −0.403, p < 0.05) and there were no differences between HDL-D parameters and HgbA1c.

3.9. Summary

VLDL, IDL, and LDL total mass was substantially reduced in both diabetic men and woman, primarily because of reduced particle numbers. All lipids were reduced in these subfractions except for LDL TG in women. All particles in both genders were depleted of CE. Total HDL mass was higher in both diabetic genders with lower mass in HDL-D but substantially higher mass in HDL-L. The entire increase in HDL mass was caused by an increase in LpA-I since the total apoA-II was slightly lower in the diabetic groups. There were no differences in the HDL-D LpA-I in either gender. Men had increased LpA-I in both HDL-L and HDL-M while the women had an increase in LpA-I only in HDL-L. There was a shift of the LpA-I:A-II particles in both genders from HDL-D to HDL-L in diabetic patients. All of the HDL particle cores were enriched in cholesterol ester except for HDL-D in women while there were minimal differences in surface lipids. In both men and women, there were increases in apoM in HDL-L and HDL-M.

4. Discussion

ApoB-containing lipoproteins in these patients were dramatically different and all in, what would typically be considered, a less atherogenic direction. Total mass of each subfraction was reduced primarily by reductions in particle number. In addition, each particle had less CE relative to both apoB and TGs as well as less apoC-III. The only parameter that could be considered detrimental was the slightly smaller IDL and LDL volumes. However, these smaller volumes were likely the result of substantial reductions (~30–60%) in total mass of each subfraction.

Table 7
HDL-M Composition (Mean + SEM).

	Women				Correlations: all women					Men				Correlations: all men				DM women vs. men	
HDL-M	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	HDL-M	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	p-value	%Diff
Total cholesterol	0.804 ± 0.167	0.757 ± 0.163	ns	−6%	–	–	–	–	Total cholesterol	0.624 ± 0.178	0.654 ± 0.140	ns*	5%	–	–	–	−7.6	0.002	16%
Free cholesterol	0.175 ± 0.043	0.182 ± 0.046	ns	4%	–	–	–	–	Free cholesterol	0.133 ± 0.037	0.147 ± 0.042	ns*	11%	–	10.7	–	−9.7	<0.001	24%
Phospholipids	0.688 ± 0.189	0.702 ± 0.159	ns	2%	–	–	–	–	Phospholipids	0.568 ± 0.159	0.586 ± 0.113	ns	3%	–	–	–	–	<0.001	20%
Triglyceride	0.066 ± 0.023	0.049 ± 0.021	0.005	−26%	−24.0	−10.5	–	–	Triglyceride	0.071 ± 0.019	0.046 ± 0.017	<0.001	−35%	–	–	−24.3	9.4	ns	7%
Cholesterol ester	0.862 ± 0.174	0.789 ± 0.172	ns	−8%	–	–	–	–	Cholesterol ester	0.673 ± 0.198	0.695 ± 0.151	ns	3%	–	–	–	–	0.008	14%
ApoA-I	41.9 ± 8.2	44.6 ± 11.6	ns	6%	–	–	–	10.1	ApoA-I	34.3 ± 7.7	44.5 ± 14.6	0.005	30%	–	–	–	–	ns	0%
ApoA-II	17.4 ± 4.6	18.2 ± 5.8	ns	5%	–	–	–	–	ApoA-II	16.9 ± 3.7	19.6 ± 8.1	ns	16%	–	–	–	–	ns	−7%
ApoC-III	6.24 ± 1.24	5.86 ± 1.84	ns*	−6%	–	–	–	–	ApoC-III	5.17 ± 2.22	5.36 ± 2.45	ns	4%	–	–	–	–	ns	9%
ApoC-II	0.98 ± 0.41	1.14 ± 0.47	ns	16%	–	–	–	–	ApoC-II	0.92 ± 0.37	1.23 ± 0.58	0.034	34%	–	–	–	–	ns	−7%
ApoC-I	5.84 ± 1.39	5.30 ± 1.88	ns*	−9%	–	–	–	–	ApoC-I	4.65 ± 1.36	5.98 ± 2.67	0.040	29%	–	–	–	–	ns	−11%
ApoM**	0.583 ± 0.371	0.943 ± 0.292	<0.001	62%	10.8	6.6	–	–	ApoM**	0.528 ± 0.226	0.850 ± 0.347	<0.001	61%	–	–	12.6	−8.4	ns	11%
LpA-I	18.6 ± 7.9	20.4 ± 8.2	ns	10%	–	–	–	–	LpA-I	11.8 ± 5.8	18.4 ± 7.5	<0.001	56%	–	6.7	–	–	ns	11%
apoA-II/apoA-I	0.425 ± 0.106	0.412 ± 0.100	ns	−3%	–	–	–	–	apoA-II/apoA-I	0.501 ± 0.101	0.439 ± 0.086	0.013	−12%	–	–	–	–	ns	−6%
apoC-III/apoA-I	0.154 ± 0.041	0.133 ± 0.033	0.032	−14%	–	–	11.1	–	apoC-III/apoA-I	0.150 ± 0.043	0.123 ± 0.038	0.013	−18%	–	–	–	–	ns	8%
apoC-II/apoC-III	0.161 ± 0.070	0.198 ± 0.063	0.034	23%	–	–	–	–	apoC-II/apoC-III	0.184 ± 0.070	0.245 ± 0.089	0.009	33%	–	–	12.6	–	0.005	−19%
Chol ester/apoA-I	20.6 ± 1.7	18.4 ± 4.8	0.039	−11%	−7.3	–	–	14.2	Chol ester/apoA-I	19.5 ± 2.3	16.3 ± 3.8	<0.001	−16%	–	–	–	–	0.032	13%
Chol ester/Trig	14.7 ± 5.7	18.9 ± 8.8	0.046	29%	20.5	9.8	–	–	Chol ester/Trig	10.4 ± 4.8	17.2 ± 7.4	<0.001	65%	–	–	23.0	−10.9	ns	10%
F Chol/Phosphol	0.314 ± 0.354	0.26 ± 0.037	ns	−17%	–	–	–	–	F Chol/Phosphol	0.234 ± 0.025	0.250 ± 0.043	ns*	7%	–	8.9	–	–	ns	4%
Total mass	258 ± 46	263 ± 58	ns	2%	–	–	–	6.0	Total mass	216 ± 49	251 ± 66	0.037	16%	–	–	–	–	ns	5%
Volume/apoA-I	208 ± 11	200 ± 23	ns	−4%	−8.8	–	–	−10.6	Volume/apoA-I	211 ± 10	191 ± 18	<0.001	−9%	–	–	−9.8	–	0.033	5%

(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoA-I) (r2 × 100)

**Insulin units (see Methods) *p < 0.05 in non-statin users

(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoA-I) (r2 × 100)

**Insulin units (see Methods) *p < 0.05 in non-statin users

Table 8
HDL-D Composition (Mean + SEM).

HDL-D	Women				Correlations: all women				HDL-D	Men				Correlations: all men				DM women vs. men	
	Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin		Controls	Diabetic	p-value	%Diff	LPL	Adipon	HL	Leptin	p-value	%Diff
Total cholesterol	0.218 ± 0.054	0.159 ± 0.049	<0.001	−27%	−12.9	−8.3	15.0	–	Total cholesterol	0.216 ± 0.040	0.169 ± 0.050	0.001	−22%	–	−6.9	–	–	ns	−6%
Free cholesterol	0.062 ± 0.016	0.055 ± 0.019	ns	−11%	–	–	–	–	Free cholesterol	0.062 ± 0.019	0.054 ± 0.017	0.099	−13%	–	–	–	–	ns	2%
Phospholipids	0.206 ± 0.043	0.159 ± 0.043	<0.001	−23%	−16.4	−11.1	7.3	–	Phospholipids	0.205 ± 0.042	0.164 ± 0.040	<0.001	−20%	–	–	−14.4	–	ns	−3%
Triglyceride	0.024 ± 0.015	0.015 ± 0.006	<0.001	−38%	−10.2	−8.2	–	–	Triglyceride	0.026 ± 0.008	0.013 ± 0.006	<0.001	−50%	–	–	−16.3	9.0	ns	15%
Cholesterol ester	0.215 ± 0.060	0.142 ± 0.062	<0.001	−34%	−17.1	−7.2	16.3	–	Cholesterol ester	0.211 ± 0.046	0.158 ± 0.068	0.002	−25%	–	−10.3	–	–	ns	−10%
ApoA-I	19.0 ± 4.5	17.8 ± 5.9	ns	−6%	–	−7.5	10.8	–	ApoA-I	20.7 ± 2.7	20.6 ± 8.0	ns	0%	–	−8.5	–	–	0.059	−14%
ApoA-II	5.39 ± 2.53	4.04 ± 1.81	0.015	−25%	−7.1	−14.1	–	–	ApoA-II	6.09 ± 1.75	5.08 ± 2.70	ns*	−17%	–	−9.0	−9.8	–	0.036	−20%
LpA-I	8.40 ± 3.87	8.98 ± 3.43	ns	7%	–	–	–	–	LpA-I	8.48 ± 2.73	10.49 ± 4.19	0.055	24%	–	–	–	–	ns	−14%
apoA-II/apoA-I	0.281 ± 0.098	0.227 ± 0.072	0.013	−19%	−7.0	−9.5	–	–	apoA-II/apoA-I	0.293 ± 0.066	0.238 ± 0.061	0.002	−19%	–	–	−9.0	–	ns	−5%
Chol ester/apoA-I	11.3 ± 1.4	7.92 ± 2.87	<0.001	−30%	−21.8	–	8.8	–	Chol ester/apoA-I	10.2 ± 1.8	7.7 ± 2.7	<0.001	−25%	–	–	–	–	ns	3%
Chol ester/Trig	10.2 ± 3.7	10.7 ± 5.1	ns	5%	–	–	–	–	Chol ester/Trig	9.1 ± 3.9	16.1 ± 13.5	0.026	78%	–	–	–	–	0.014	−34%
F Chol/Phosphol	0.302 ± 0.064	0.360 ± 0.133	0.060	19%	24.1	–	–	–	F Chol/Phosphol	0.303 ± 0.065	0.344 ± 0.128	ns*	14%	–	8.9	9.2	–	ns	5%
Total mass	95.2 ± 22.2	82.6 ± 25.1	0.050	−13%	−8.3	−11.5	12.2	–	Total mass	101.4 ± 14.5	93.8 ± 31.8	ns	−7%	–	−9.9	−7.8	–	0.069	−12%
Volume/apoA-I	164 ± 7	151 ± 12	<0.001	−8%	−19.6	–	–	–	Volume/apoA-I	160 ± 8	148 ± 12	<0.001	−8%	–	–	−10.7	–	ns	2%

(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoA-I) (r2 × 100)

(Lipids: mmol/l; apolipoproteins: nmol/l; mass: mg/dl; volume: nM3 of lipid + apolipo/nM apoA-I) (r2 × 100)

*p < 0.05 in non-statin users

The magnitude of these differences can be seen with medication therapy and, in fact, more diabetic patients were on statins. However, when only non-statin users were analyzed the differences were the same or greater, such that statin use appears to have reduced the differences between patients and controls but they obviously did not eliminate them. There are several possible explanations for the lack of statin effects. First, statins have fairly minimal impact on many of the parameters that we measured. Second, patients may have been on low dose or weak statins. Third, the patients may have been non-compliant with the statins. In addition, diabetic groups had more obese individuals. As expected, BMI was positively correlated with TGs, apoB, VLDL-TG, and LDL-C but negatively correlated with HDL-C and apoA-I. Therefore, beneficial lipoprotein parameters were present despite more obesity. Similarly, hyperglycemia as determined by HgbA1c had detrimental lipoprotein effects such that the substantial beneficial differences that we saw occurred despite hyperglycemia. Men had substantially greater absolute and percent reductions than women so essentially all measured parameters were the same in diabetic men and women. Conversely, control women had lower concentrations of these lipoproteins than control men. Reductions in apoB-containing lipoproteins in our population were substantially greater than those seen in previous studies.

HDL-L showed the greatest percent differences in both genders, with men again showing the greatest difference. However, in this case, the women maintained their significant advantage. These differences are qualitatively similar to previous studies where HDL_2 was increased in T1DM (HDL-L is similar to traditional HDL_2) (Verges, 2009). Both LpA-I and LpA-I:A-II were increased in HDL-L but LpA-I was the dominate contributor similar to previous studies (Kahri et al., 1993). There were also dramatic increases in apoM, a protein that may be important for cholesterol exchange with cells (Hu, Zheng, & Wang, 2010; Ooi et al., 2010). HDL-L was enriched in CE relative to TGs but the lipid to apoA-I ratios were lower for all four lipids in the diabetic patients.

Increased HDL-L LpA-I can be caused by more efficient maturation from smaller, denser particles. This maturation typically requires lipoprotein lipase (LPL) but is inhibited or reversed by cholesterol ester transfer protein (CETP) and/or hepatic lipase. Increased LPL did have a substantial impact on HDL-L in women while men had a lesser effect from reduced HL. In addition, reduced CE concentrations in apoB-containing particles coupled with increases in HDL-L suggest reduced CETP activity in both genders. More efficient maturation of LpA-I should promote reverse cholesterol transport. However, if particle clearance is compromised by diabetes (for example, by reduced SR-B1 activity De Boer et al., 2012) then these particles would accumulate and reverse cholesterol transport would be reduced.

HDL-M shows a gender difference in that diabetic women were similar to controls with the exception of increased apoM and reduced triglycerides. Men, on the other hand, had increased LpA-I (+30%) and total mass (+16%) with reduced lipid to apoA-I ratios, similar to those seen in HDL-L. Their increase in apoM was similar to the women. LpA-I:A-II is found primarily in HDL-M but it was not affected by diabetes in either gender. Conversely, HDL-D LpA-I:A-II was reduced in both genders by approximately the same absolute amount as it was increased in HDL-L, suggesting a maturation of these particles from HDL-D to HDL-L. HDL-D LpA-I was only marginally increased in diabetic men. The most obvious modification seen in HDL-D was the lipid depletion of these particles. In both men and women, CE, PL, and TG to apoA-I ratios were reduced. Typically, when there are substantial increases in HDL-L, we see reductions in HDL-D, suggesting rapid metabolism to the larger particles. However, these findings may also reflect poor efflux of lipids from cells onto these particles.

Diabetic women had a 2-fold increase in LPL while HL was reduced by half. Men, on the other hand, had no change in LPL and only a marginal increase in HL. A likely explanation for the increase in LPL in the women is the hyperinsulinemia typical of insulin-treated T1DM

(Verges, 2009) but then men should have had a similar increase. However, men tend to have less subcutaneous fat than women and men with T1DM tend to have even less (Langer, Lindholm, Orndahl, & Bjorntorp, 1975). Therefore, men may not have been able to respond to the hyperinsulinemia because of a reduction in responsive tissues. Previous studies have reported increases in LPL in both genders (Kahri et al., 1993; Nikkila & Hormila, 1978).

Hepatic lipase is typically not affected by T1DM but it has been occasionally reported to be reduced (Rosental et al., 1995). Therefore, the substantial reductions in women in our study as well as the trend toward an increase in the men are atypical. HL is reduced by estradiol (Deeb, Zambon, Carr, Ayyobi, & Brunzell, 2003) so the lower activity in women was expected. Intraperitoneal (IP) insulin therapy (which increases portal insulin concentrations) has been shown to increase HL activity in T1DM (Ruotolo et al., 1194) and was associated with the expected reduction in HDL_2 and increase in HDL_3. These data suggest that portal insulin deficiency in T1DM may be playing a role in the reduction of HL in the women. However, the HL activity in IP treated patients was substantially higher than non-diabetic controls while HL activity in these patients while treated with subcutaneous insulin was similar to controls. There are no reports of insulin having a direct effect on HL activity, however, it has been reported that HL activity is inversely correlated with adiponectin (Clarenbach et al., 2007). Because adiponectin is highly correlated with body composition, there is the possibility that differences in body composition are responsible for the variances in HL even though we could not demonstrate a correlation between HL and adiponectin in our population at the time of sampling.

LPL activity was not correlated with any lipoprotein parameters in men and, surprisingly, it had no measurable impact on TG and VLDL concentrations in women. However, it did have a small, negative impact on IDL and LDL lipids. This suggests an increased clearance of these particles through LPL-receptor activity since its enzymatic activity alone would be expected to increase the concentrations of these particles. LPL did have a dramatic, positive effect on all components of HDL-L with a complementary negative effect on HDL-D as would be expected (Lewis & Radar, 2005). This positive effect was primarily on LpA-I since apoA-II was only modestly increased in HDL-L. In addition, LPL activity had a similar, dramatic impact on the increase in apoM in HDL-L with a lesser impact in HDL-M.

The lower HL activity in the diabetic women had a small impact on their lower LDL CE and VLDL components. Even though its impact on VLDL was small, it was greater than the other measured parameters. It is unclear how the fall in HL contributed to the reduction in VLDL but the fall would be expected to reduce the conversion of IDL to LDL contributing to the fall in LDL-CE. The lower HL activity also contributed to increases in HDL-L PL, TG, apoA-I, and LpA-I with reciprocal reductions in HDL-D CE, PL, apoA-I, and total mass. These are the expected results of reduced conversion of HDL-L to HDL-D with less lipase activity and reduced particle clearance because of lower receptor activity (Deeb et al., 2003).

The slightly higher HL in diabetic men contributed to the fall in TGs, VLDL/IDL lipids, and apoB which can be explained by both increased lipase and receptor activity. HL typically has more impact on smaller lipoprotein particles and we saw a somewhat greater effect on IDL than on VLDL but it had minimal effects on LDL and then only on TGs. HL activity was negatively correlated with HDL-D TGs and PL as expected but it was positively correlated with most HDL-L components. This correlation was unexpected and unlikely to be a direct effect on HDL. It was more likely the result of lower VLDL and IDL which typically leads to increased HDL-L.

Adiponectin secretion is increased as fat cells shrink but is also increased by insulin, adenosine (Szkudelski, Nogowski, & Szkudelska, 2011), nitric oxide (Koh et al., 2010), and PPARg agonists (Liu & Liu, 2012). It is inhibited by epinephrine, cAMP (Szkudelski et al., 2011), oxidative stress, TNFa (Mondal et al., 2012), and overfeeding (Liu & Liu, 2012). T1DM patients typically have increased oxidative stress and TNFa but low levels of nitric oxide (Giacco & Brownlee, 2010) which should reduce adiponectin. It is likely; therefore, that peripheral hyperinsulinemia and reduced fat cell size were the primary causes of increased adiponectin. Adiponectin has been shown to increase muscle LPL activity (Qiao, Zou, van der Westhuyzen, & Shao, 2008) and the synthesis of apoA-I and ABCA1 (Oku et al., 2007). In addition, transgenic mice overexpressing adiponectin in macrophages have elevations of hepatic apoA-I, apoB, apoE, LDL receptor, and ABCG-1 mRNA while SREBP-1, PCSK9, and HMG-CoA reductase are reduced (Luo et al., 2011). Similar to our patients, these animals had reductions of >30% in LDL-C and VLDL-C while HDL-C was increased 41%. Clearly, elevated adiponectin would be predicted to lower atherogenic lipoproteins while improving reverse cholesterol transport. In addition, adiponectin directly inhibits several steps of atherogenesis (Fantuzzi & Mazzone, 2007).

Leptin was reduced in T1DM men which typically reflects a reduction in fat cell size. Reduced leptin lowers hepatic AMP-kinase activity and fatty acid synthesis (Harwood, 2012) which reduces VLDL secretion, contributing to the reduced VLDL/IDL lipids that we saw. Reductions in VLDL/IDL lipids typically increase HDL-C (as seen in HDL-L) and reduce HDL-TG (as seen in HDL-M and HDL-D). In addition, leptin correlates positively with cholesterol ester transfer protein activity (Dullaart, de Vries, Dallinga-Thie, van Tol, & Sluiter, 2007) and reduced CETP would produce similar HDL changes.

In summary, the lipoprotein composition and adipokine concentrations as well as the lipase activities in the women would be expected to reduce atherosclerotic risk in T1DM. The only adverse finding that we demonstrated was a non-significant increase in hepatic lipase in men. Because the lipoprotein composition does not explain their high cardiovascular risk, our data support the hypothesis that lipoprotein function is compromised in T1DM.

Author contributions

Study design, study conduct, data collection, data analysis, and data interpretation: TH, RC, SD, AM, and RG. Drafting manuscript and revising manuscript content: TH and RG. Approving final version of manuscript: TH, RC, SD, AM, and RG.

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We have published a detailed analysis of some of the total HDL cholesterol data: Calderon RM, Diaz S, Szeto A, Jose A. Llinas JA, Thomas A Hughes TA, Armando J Mendez AJ, Ronald B. Goldberg RB: Elevated Lipoprotein Lipase Does Not Account For the Association Between Adiponectin and HDL in Type 1 Diabetes. J Clin Endocrinol Metab 100(7): 2581–2588, 2015.

Context: Increased high-density lipoprotein cholesterol (HDL-C) is common in type 1 diabetes (T1D) and is associated both with hyperadiponectinemia and with elevated lipoprotein lipase activity (LPL). Because adiponectin has been shown to increase LPL expression, elevated LPL may link the hyperadiponectinemia in T1D with increased HDL.

Objective: The purpose of this study was to determine whether LPL activity accounts for the association between adiponectin and HDL in T1D.

Design: A cohort of 127 patients with T1D attending the Diabetes Clinic at the University of Miami and 103 healthy control subjects was recruited.

Main Outcome: HDL-C and adiponectin were measured in the full cohort and in a subgroup, HDL subfractions were obtained by ultracentrifugation, and LPL and hepatic lipase were measured in postheparin plasma.

Results: Total HDL-C and the lowest density HDL subfraction, apolipoprotein A-I, LPL activity, and adiponectin levels were higher in subjects with T1D than in control subjects ($p < .05$). Both adiponectin and LPL activity were directly associated with total HDL-C and its lowest density subfraction, but adiponectin and LPL were not correlated ($p = 0.13$). Adiponectin alone explained 11.6% and adiponectin plus LPL explained 23.8% of the HDL-C variance. In a multivariate model, adiponectin remained an independent predictor of HDL-C along with LPL and serum creatinine, explaining together 27% of HDL-C variance.

Conclusions: Adiponectin was strongly associated with HDL-C in T1D, suggesting that hyperadiponectinemia is linked to the elevated HDL-C in this population. However, this relationship is independent of the association between LPL and HDL-C. Thus, elevated adiponectin and LPL activity are independently related to increased HDL-C in T1D.

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