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Effect of niacin on preβ-1 high-density lipoprotein levels in diabetes

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Abstract

Preβ-1 high-density lipoprotein (HDL) is an acceptor of peripheral free cholesterol and thus a participant in reverse cholesterol transport. Because patients with diabetes may have defects in reverse cholesterol transport, we hypothesized that (1) preβ-1 HDL might be decreased in diabetes and (2) because niacin improves reverse cholesterol transport and may stimulate preβ-1 HDL maturation, niacin would further decrease steady-state levels of preβ-1 HDL in diabetes. Absolute levels of preβ-1 HDL mass were measured using an isotopic dilution-ultrafiltration assay that measures apolipoprotein (apo) A-I after physically isolating preβ-1. Plasma apo A-I concentration and routine lipids were also evaluated in 11 diabetic patients. Diabetic subjects have a nearly 50% reduction of circulating levels of preβ-1 HDL to 36 ± 22 (1 SD) μg/mL compared with our previously published values of 73 ± 44 μg/mL in 136 healthy subjects. After niacin therapy, there was a further 17% reduction of preβ-1 HDL levels to 30 ± 26 μg/mL ($P < .026$) compared with baseline. The percentage of preβ-1 HDL in diabetic patients, as a percentage of total apo A-I, was about half of the normal value of 6.1% ± 3.6%; after niacin in diabetic patients, the percentage further decreased from 3.3% ± 2.1% to 2.3% ± 1.9% ($P < .003$). Absolute levels of apo A-I were similar in diabetic patients (1.14 ± 0.29) and healthy subjects (1.24 ± 0.24), and were unchanged by niacin in diabetic patients. We conclude with the novel observations that diabetes is associated with significantly reduced levels of preβ-1 HDL and that, after niacin treatment, a further lowering of preβ-1 HDL levels occur. Several altered mechanisms of RCT in diabetes are consistent with low levels of preβ-1 HDL both before and after niacin treatment.

1. Introduction

High-density lipoproteins (HDLs) are known to have antiatherogenic properties involving roles in reverse cholesterol transport (RCT) and a variety of other activities [1]. Nascent HDL refers to the entrance of various molecular forms of apolipoprotein (apo) A-1 into the plasma compartment, or intracellular apo A-1 associated with other macromolecules, for example, very low-density lipoprotein (VLDL), that are about to be secreted into the plasma. Nascent HDL, as observed in media from cell-cultured systems, represents apo A-1 particles that are free, poorly lipidated, or discoidal shaped [2]. Mouse liver perfusate data, however, indicate that no free apo A-1 is secreted because there is no free apo A-1 in the perfusate [3]. In mammalian liver, apo A-1 is present in the Golgi compartment associated with VLDL and is thought to subsequently be shed, along with phosphatidyl ethanolamine and other lipids, as nascent HDL after entry of these larger lipoproteins into the plasma [4] (Fig. 1). Similar events occur in the intestine with chylomicrons [5,6]. This nascent HDL is thought to quickly organize into particles of preβ-1 HDL: a particle with a molecular weight of circa 67 kd; containing 2 molecules of apo A-1; and about 10% to 20% by weight of lipids, comprising free cholesterol and phospholipid. In human plasma, the particles representing free apo A-1 or discoidal-shaped, lipidated apo A-1 are extremely rare compared with preβ-1 HDL, which represents about 5% of total HDL species (Ren, Ishida, and Kane; unpublished observations using digitally enhanced cryoelectron microscopy).

Once in plasma, preβ-1 can serve as a precursor to slightly larger, preβ migrating HDL species for example, preβ-2, -3, and -4, or be eliminated by the kidney (Fig. 1). Preβ-1 HDL is an acceptor of free cholesterol from a variety of peripheral tissues, including endothelium, and is thus a

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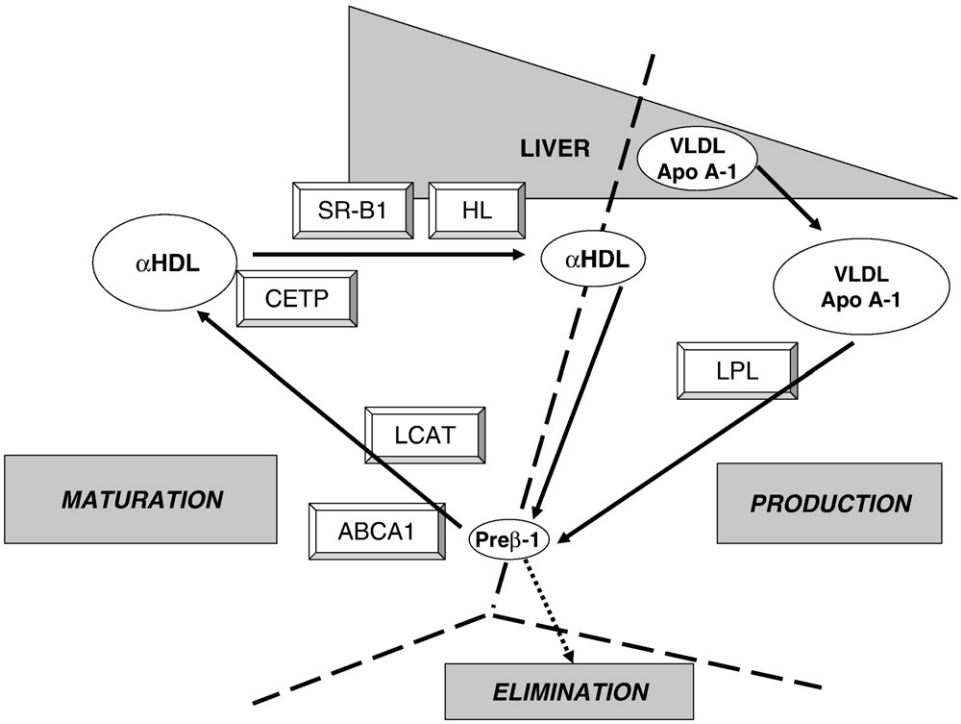

Fig. 1. The central role of pre*β*-1 HDL in HDL metabolism and RCT. The dashed lines delineate between the production, maturation, and excretion phases of pre*β*-1 HDL. Each of these pathways is described in detail in the text. LPL indicates lipoprotein lipase; HL, hepatic lipase.

key participant in RCT. As pre*β*-1 HDL is remodeled and matures to larger pre*β* migrating species, phospholipid transfer protein (PLTP) can mediate transfer of phospholipids from VLDL and other phospholipid-rich lipoproteins to these pre*β* species. Free cholesterol within pre*β* HDL species is esterified by lecithin:cholesterol acyltransferase (LCAT), further promoting the maturation of pre*β* HDL species into larger α-migrating HDL particles. These α-migrating HDL particles can present cholesteryl esters to the liver or transfer cholesteryl esters to other triglyceride (TG)-rich lipoproteins for eventual removal by the liver, thus completing the RCT process.

Thus, pre*β*-1 HDL appears to be the central particle of the HDL system as shown in Fig. 1: (*a*) being formed after release of nascent HDL from larger non-HDL lipoproteins and from larger-diameter HDL particles when the latter particles are subjected to transfer reactions, such as by cholesteryl ester transfer protein (CETP) or by interactions with the scavenger receptor B-1 (SR-B1) receptor in the production phase; (*b*) acting as a quantum particle in the maturation phase leading to new, larger molecular species; and (*c*) being excreted by the kidney when the maturation phase has diminished activity relative to production.

Diabetic patients and insulin-resistant subjects have many abnormalities of HDL remodeling and RCT. In diabetic patients, the lack of insulin stimulation and hyperglycemic suppression of hepatic apo A-I gene expression may reduce hepatic apo A-1 production [7]. In diabetes, excessive release of free fatty acids (FFA) is mediated by intracellular adipocyte lipases. High levels of circulating FFA then result in increased intracellular levels of unsaturated fatty acids in liver and macrophage that down-regulate the expression of adenosine triphosphate–binding cassette transporter A1 (ABCA1), which reduces pre*β*-1 HDL-mediated cholesterol uptake from peripheral cells [8], thus increasing the likelihood of renal elimination. A similar reduction in ABCG1 expression has been reported in diabetic patients [9]. Previous studies have shown increased PLTP activity in insulin-resistant syndromes and diabetes that could result in accelerated pre*β*-1 HDL removal via maturation into larger HDL species [10,11]. Finally, TG-enriched α HDL species produced by CETP can be converted by elevated levels of hepatic lipase, observed in diabetes, to smaller HDL species ultimately suitable for elimination [12]. Each of these above processes led us to hypothesize that pre*β*-1 HDL is decreased in diabetes.

Niacin is effective in reversing several abnormalities of HDL remodeling and RCT observed in diabetes, and each could affect circulating levels of pre*β*-1 HDL. Niacin reduces apo A-I and HDL catabolism by inhibiting HDL holoparticle receptor uptake [13]; this process could be compensated for by increased SR-B1 activity to remove cholesteryl esters, thus resulting in smaller HDL species, including pre*β*-1 HDL, which could be eliminated by the kidney. Niacin also enhances ABCA1 gene expression indirectly by reducing circulating FFA [14]; this mechanism could increase maturation of pre*β*-1 HDL, thus lowering its circulating levels. Finally, niacin reduces intrahepatic VLDL produc-

tion, thus potentially limiting plasma-generated preβ-1 HDL from TG-rich lipoproteins [15]. These observations of niacin activity led us to hypothesize that niacin could further reduce preβ-1 HDL levels in diabetic subjects.

There are no studies measuring absolute preβ-1 HDL levels in diabetic patients. In this study, we measured absolute levels of preβ-1 HDL and the percentage of apo A-I represented by preβ-1 HDL in diabetic patients before and after treatment with niacin.

2. Materials and methods

2.1. Patients

Eleven type 2 diabetes mellitus patients, 9 men and 2 women, with a mean age of 62 years were evaluated (Table 1). Patients consumed a mean dose of 2886 mg/d of extended-release (ER) niacin as shown in Table 1 (Niaspan; Abbott Laboratories, Abbott Park, IL) in an attempt to convert these low-density lipoprotein (LDL) phenotype B patients to phenotype A or reduce the small dense LDL concentration to normal at about 20 mg/mL or increase HDL-2 levels to about the normal level of 40% of the total HDL (Table 2) [16]. Mean duration of maintenance therapy was 6 months. The mean hemoglobin A_{1c} level in these patients before treatment with niacin was 5.9% ± 0.5% (1 SD) as shown in Table 1. All subjects signed an informed consent approved by an institutional review board before participation.

This open-label, uncontrolled, efficacy study used retrospective analyses after aggressive lipid-lowering treatment both before and during ER niacin treatment. All subjects took niacin as outpatients, once daily. Initial doses were 500 to 750 mg, taken 1 to 2 hours after dinner, with continuous escalation of doses over a period of 1 to 4 months. Detailed instructions were given regarding the timing of the niacin dose; timing was further customized to each patient if adverse effects were significant. Patients were asked to monitor their blood glucose levels 2 to 4 times daily. Attempts were made to modify niacin-induced hyperglycemia by increasing oral hypoglycemic agents or insulin dosages. Active titration of oral agents and/or insulin is essential to maintain optimal glycemic status. None of the patients received thiazolidinediones (naive), fibrates, cerivastatin, or atorvastatin during the observation period. Patients were permitted use of simvastatin or pravastatin 10 to 40 mg daily (Table 1). At these doses in diabetes, we have previously reported no changes in total HDL cholesterol (HDL-C), HDL-2, small dense LDL cholesterol (LDL-C) concentration, and LDL average peak particle size [17]. Statin doses were not altered during niacin use.

Table 1
Diabetic patient characteristics

Patient	Age (y)	Sex	Statin (dose in mg)	ER niacin (mg/d)	Hemoglobin A_{1c} (%)	
					Pre	Dur
1	64	M	Pravastatin 40	3000	6.1	6.3
2	69	M	Pravastatin 40	3750	5.9	7.0
3	62	M	Simvastatin 10	1500	6.6	6.3
4	74	M	Pravastatin 40	4000	5.2	5.5
5	74	F	Pravastatin 40	2250	5.7	5.2
6	57	F	Pravastatin 40	3000	6.3	6.7
7	65	M	Pravastatin 40	3000	6.5	6.1
8	58	M	Pravastatin 40	3000	5.5	6.2
9	47	M	Pravastatin 40	2250	6.3	6.7
10	56	M	Simvastatin 10	3000	5.8	5.9
11	58	M	None	3000	5.2	6.3
				Mean	5.9	6.2
				1 SD	0.5	0.5
				P value	.12	

2.2. Biochemical analyses

Plasma samples for lipid and lipoprotein analyses were prepared from EDTA-treated blood within 30 minutes at 4°C and then frozen at −80°C until analysis. Triglyceride and lipoprotein cholesterol values (HDL-C) were measured enzymatically (Cholestech Instruments, Hayward, CA). Identification and densitometric measurements of LDL and HDL species were performed using 2% to 16% polyacrylamide gradient gel electrophoresis of plasma samples as previously described in detail [17]. Small dense LDL-C concentrations were calculated from the percentage of small dense LDL on the gels and total LDL-C as previously described [17].

Preβ-1 HDL was measured by isotope dilution-ultrafiltration [18]. Briefly, isotopically labeled preβ-1 HDL was prepared as follows. The total apo A-I–containing lipoprotein fraction was sequestered from normal human plasma by selective affinity immunosorption. The preβ-1 HDL fraction was separated from other apo A-I lipoproteins by electrophoresis in starch block, avoiding the lipoproteins of the anodic shoulder of the preβ HDL peak that contain preβ lipoprotein species of higher molecular weight. Purity of the preβ-1 lipoproteins was verified by electrophoresis in 3% to 34% nondenaturing gradient acrylamide gels, where the apparent molecular weight was 67 kd, and by demonstration of preβ electrophoretic mobility in nongradient agarose gel electrophoresis. The preβ-1 HDL to be used as the dilution probe was labeled as a tritiated adduct using *N*-succinimidyl [2,3-H^3] propionate (Amersham, Piscataway, NJ) coupled to α and ε amino groups of the apo A-1 protein. The unbound label was removed by extensive dialysis at 0°C. A labeled probe sample was added to plasma samples at 0°C with gentle but thorough mixing. The diluted preβ-1 HDL pool of plasma was sampled by ultrafiltration using a centrifugal ultrafilter that discriminates between preβ-1 HDL and other apo A-I–containing lipoproteins (Microcon-100, Amicon, Billerica, MA). The specific activity of the ultrafiltrate was determined by scintillation counting, and the apo A-I contents of the plasma and ultrafiltrate were measured by an enzyme-linked immunosorbent assay technique developed to quantitate apo

Table 2
Effect on ER niacin of lipid parameters before and during treatment

Patient	TG (mg/dL)		LDL-C (mg/dL)		LDL size (Å)		Small dense LDL (mg/dL)		Total HDLC (mg/dL)		HDL-2 (% of total HDL)	
	Pre	Dur	Pre	Dur	Pre	Dur	Pre	Dur	Pre	Dur	Pre	Dur
1	126	80	199	71	248	251	78	23	29	39	14	23
2	239	79	163	63	245	266	82	14	28	47	28	38
3	64	45	96	73	260	267	–	9	56	66	54	45
4	152	82	130	63	247	251	71	30	36	42	22	36
5	243	148	157	60	249	264	69	8	62	100	63	91
6	312	108	123	98	249	264	71	16	43	65	28	35
7	137	75	93	47	256	265	26	3	28	57	31	39
8	143	95	126	93	256	267	24	10	42	58	22	26
9	158	107	108	108	257	268	30	4	41	44	21	21
10	193	96	209	110	260	270	26	13	69	75	23	52
11	303	251	132	173	244	247	–	2	33	43	30	15
Mean	188	106	140	87	252	262	53	12	43	58	31	38
1 SD	78	55	39	35	6	8	25	8	14	18	15	21
P value	<.0003		<.004		<.02		<.0005		<.005		<.062	

Patient	Apo A-I (mg/mL)		Preβ-1 HDL (μg/mL)		Preβ HDL (% of total apo A-1)	
	Pre	Dur	Pre	Dur	Pre	Dur
1	0.64	0.78	22.7	9.60	3.55	1.23
2	1.20	1.00	27.4	9.60	2.28	0.96
3	1.38	1.36	13.1	11.8	0.95	0.87
4	0.95	1.25	29.2	18.0	3.07	1.44
5	1.17	1.62	32.2	17.4	2.75	1.07
6	1.10	1.36	56.6	65.3	5.15	4.80
7	0.92	1.13	36.5	19.4	3.97	1.72
8	1.27	1.12	11.6	13.2	0.91	1.18
9	1.33	1.15	20.4	17.1	1.53	1.49
10	1.70	1.54	70.4	63.6	4.14	4.11
11	0.90	1.27	73.5	80.3	8.17	6.32
Mean	1.14	1.24	35.8	29.6	3.32	2.29
1 SD	0.29	0.24	21.7	26.3	2.10	1.88
P value	.12		.026		.003	

A-I equally in α and preβ-1 HDL species. The content of preβ-1 HDL in plasma was then calculated by the isotope dilution equation:

$$\frac{\text{Probe radioactivity added}}{\text{Specific activity of ultrafiltrate}} = \text{mass of original prebeta}-1 \text{ HDL pool in plasma}$$

All measurements were made in duplicate. Paired values that did not agree within 10 μg/mL were repeated. Values were rejected if final duplicates did not agree within 10 μg/mL, and the coefficient of variation for the assay was 3%. Preβ-1 HDL levels were expressed as absolute concentration levels (micrograms per milliliter) of preβ-1 HDL apo A-I and as the percentage of total plasma apo A-I represented by preβ-1 HDL.

Hemoglobin A_{1c} was measured using the DCA 2000 (Abbott Diagnostics, Pittsburgh, PA) and the Bio-Rad Variant (Bio-Rad, Richmond, CA) assays with all data normalized to the Diabetes Control and Complication Trial format; thus, all values are comparable [19].

2.3. Statistical analyses

All data are presented as mean ± 1 SD. Paired *t* tests were used to determine significance. For all HDL, TG, and preβ-1 HDL determinations, the observed values were transformed to the natural logarithms before statistical assessment.

3. Results

To assess preβ-1 HDL changes in the context of other relevant lipids and lipoproteins, 11 diabetic patients were evaluated for the effects of ER niacin on TG, LDL-C, small dense LDL, apo A-I, and other HDL species. Total TG and LDL-C were decreased by niacin as shown in Table 2. Small dense LDL-C was decreased 77% by niacin as shown in Table 2. Although higher mean levels of apo A-I occurred in

Table 3
Mean apo A-I and preβ-1 HDL values in healthy subjects

Subjects (n)	Apo A-I (mg/mL)	Preβ (% of total apo A-I)	Preβ (μg/mL)
All (136)	1.23 ± 0.30	6.1 ± 3.6	73 ± 44
Women (90)	1.25 ± 0.31	5.5 ± 3.3	68 ± 40
Men (46)	1.16 ± 0.27	7.2 ± 4.0	84 ± 49

niacin-treated patients, the changes were not significant. We also evaluated the effects of niacin on total HDL-C and HDL-2 in the context of preβ-1 HDL before and after treatment. Total HDL-C levels in diabetic subjects using niacin were increased by 36% as shown in Table 2. Percentage of HDL-2, as a percentage of total HDL-C, increased by 23%; but that was only a trend as shown in Table 2.

The mean preβ-1 HDL concentration in diabetic patients was low, 36 μg/mL, before niacin treatment (Table 2). Our mean preβ-1 HDL concentration in nondiabetic subjects was 73 μg/mL as previously reported [20] (Table 3). Mean preβ-1 HDL was decreased 17% further after niacin use in diabetic patients. Percent preβ-1 HDL, as a percentage of total apo A-I, was also decreased by 31% as shown in Table 2.

To evaluate the effects of niacin on glycemic control, we measured the mean hemoglobin A_{1c} before and after niacin. There was no change in A_{1c} between the baseline mean and the posttreatment mean as shown in Table 1.

4. Discussion

Our major new findings are as follows: (1) diabetic subjects, during quite acceptable glucose control, have 50% lower circulating levels of preβ-1 HDL compared with values observed in healthy subjects from our previously published studies; and (2) diabetic subjects treated with ER niacin have a 17% further reduction of preβ-1 HDL levels compared with their baseline levels. Both of these observations are consistent with our 2 hypotheses described in the "Introduction."

We found baseline mean circulating preβ-1 HDL level of 36 μg/mL in diabetic patients, which is substantially lower than published values in the 70- to 80-μg/mL range in healthy subjects previously reported by ourselves and presented here in Table 3 [20] and by others [21]. The decrease is even greater if adjusted for sex because most of our patients were men. The reduction of preβ-1 HDL levels as a percentage of total apo A-I reflects the marked reduction of absolute levels of preβ-1 HDL and relatively stable levels of apo A-I in our patients.

Decreased absolute preβ-1 HDL levels could be a reflection of (1) decreased production or function of preβ-1 precursors, for example, apo A-I; (2) decreased maturation into larger nonpreβ-1 HDL particles mediated by decreased ABCA1 activity; and/or 3) increased renal elimination (Fig. 1).

Diabetic patients have decreased apo A-I production by the liver, probably mediated by increased FFA, cytokines, hyperglycemia, and hypoinsulinemia [7]. Apolipoprotein A-I in diabetic patients has also been shown to have reduced ability to mediate cholesterol efflux because of excessive glycation [22]. These quantitative and functional abnormalities, in addition to increased apo A-I clearance [23], could in part contribute to decreased circulating levels of preβ-1 HDL. Although, in our small group of patients, circulating apo A-I levels were similar to normal levels [20], others have reported lower apo A-I levels, but also in a small number of subjects with glucose intolerance [23]. These differences are probably attributed to small sample size. Decreased ABCA1 activity in diabetes could increase preβ-1 elimination via decreased maturation in larger HDL species, thus reducing circulating steady-state levels of preβ-1 particles. Thus, there are multiple mechanisms that could account for low preβ-1 HDL levels in diabetes (Fig. 1).

Both the percentage of preβ-1 HDL, as a fraction of total apo A-I, and absolute preβ-1 HDL levels were further reduced after niacin, which could be a reflection of further increased maturation or renal elimination. Niacin acutely decreases FFA release from adipose tissue, which could decrease FFA-mediated inhibition on ABCA1 gene expression [8,14]. Activation of peroxisome proliferator-activated receptor−γ by niacin also promotes expression of the ABCA1 gene product [15,24]. These niacin-mediated actions to increase ABCA1 transporter activity would enhance free cholesterol uptake by preβ-1 HDL particles, thus promoting maturation into larger preβ and then α-migrating HDL particles measured as total HDL-C, the latter of which was elevated in this study after niacin. Niacin also inhibits HDL particle uptake via the holoparticle receptor and thus increases circulating levels of α HDL particles [13]. Given the preference of large-diameter α HDL as substrate for SR-B1, this could favor hepatic uptake of cholesteryl ester by that receptor [25], resulting in the production of smaller HDL species available for renal elimination. Finally, niacin reduces hepatic VLDL production, thus limiting plasma-generated preβ-1 HDL from TG-rich lipoproteins, which further contributes to lower preβ-1 HDL levels after niacin.

The physiologic and cardiovascular (CV) risk relevance of the low (absolute or relative) preβ-1 HDL levels in diabetes, and further lowering induced by niacin, becomes clearer when considering preβ-1 HDL as the quantum particle of the HDL RCT system. For this reason, the apparent small changes in levels of this particle species relative to other HDL species, such as the cholesteryl ester–rich HDL-2 and HDL-3 species, afford insight as to the formation and removal of large-diameter HDL species within the system by LCAT, CETP, and other mechanisms. Despite low circulating amounts of preβ-1 HDL, its turnover time is very short, with a half-life of 30 minutes at 37°C in vitro (Kane and Kunitake, unpublished observations). Similar rapid clearance rates and high renal uptake of preβ-1 HDL have been described recently in a human apo A-I transgenic mouse model, which provide direct support for our concepts [26].

Preβ-1 HDL thus virtually disappears by maturing into larger HDL particles mediated by PLTP and LCAT. Thus, the kinetics of the preβ-1 HDL species makes it metabolically significant despite its low absolute levels. The level of preβ-1 HDL in plasma is a steady-state value reflecting *production* by the remodeling of other lipoproteins, balanced by *maturation* of this species into larger particles and *elimination* by the kidney (Fig. 1). Thus, preβ-1 HDL serves a manometer function with respect to the RCT cycle.

Another significant feature associated with our finding of reduced levels of preβ-1 HDL in the setting of improved RCT and CV risk after niacin is a corollary we have observed and previously published in diabetic patients with low total HDL-C levels [27]. In these patients, we observed a 40% increase in the level of HDL-2 subspecies after atorvastatin treatment, yet no significant change of total HDL-C levels. Similar observations have been made in subjects with combined hyperlipidemia [28]. Thus, the kinetics of HDL subspecies metabolism is obviously an important factor in reducing CV risk; and steady-state levels of any one molecular species may not reflect overall RCT and thus CV risk.

In conclusion, the low levels of preβ-1 HDL associated with diabetes may reflect a variety of mechanisms primarily involving reduced production and decreased maturation coupled with enhanced renal elimination, most of which negatively impact RCT. After niacin treatment, the further lowering of preβ-1 HDL levels may paradoxically reflect improved RCT in diabetes due to niacin's effects on the preβ-1 HDL maturation process. Definitive studies will await production and clearance rate evaluations of the various HDL species involved in healthy and diabetic subjects.

References

[1] Borggreve SE, De Varies R, Dullaart RP. Alterations in high-density lipoprotein metabolism and reverse cholesterol transport in insulin resistance and type 2 diabetes mellitus: role of lipolytic enzymes, lecithin:cholesterol acyltransferase and lipid transfer proteins. Eur J Invest 2003;33:1051-69.

[2] Chisholm JW, Burleson ER, Shelness S, Parks JS. ApoA-I secretion from HepG2 cells: evidence for the secretion of both lipid-poor apoA-I and intracellularly assembled nascent HDL. J Lipid Res 2002;43: 36-44.

[3] Hamilton RL, Williams MC, Fielding CJ, Havel RJ. Discoidal bilayer structure of nascent high density lipoproteins from perfused rat liver. J Clin Invest 1976;58:667-80.

[4] Hamilton R, Moorehouse LA, Havel RJ. Isolation and properties of nascent lipoproteins from highly purified rat hepatocytic Golgi fractions. J Lipid Res 1991;32:529-43.

[5] Imaizumi K, Havel RJ, Fainaru M, Vigne J-L. Origin and transport of the A-l and arginine-rich apolipoproteins in mesenteric lymph of rats. J Lipid Res 1978;19:1038-46.

[6] Vigne J-L, Havel RJ. Metabolism of apolipoprotein A-I of chylomicrons in rats and humans. Can J Biochem 1981;59:613-8.

[7] Mooradian AD, Haas MJ, Wong NCW. Transcriptional control of apolipoprotein A-1 gene expression in diabetes. Diabetes 2004;53: 513-20.

[8] Uehara Y, Engel T, Li Z, Goepfert C, Rust S, Zhou X, et al. Polyunsaturated fatty acids and acetoacetate downregulate the expression of the ATP-binding cassette transporter A1. Diabetes 2002;51:2922-8.

[9] Mauldin JP, Nagelin MH, Wojcik AJ, Srinivasan S, Skaflen MD, Ayers CR, et al. Reduced expression of ATP-binding cassette transporter G1 increases cholesterol accumulation in macrophages of patients with type 2 diabetes mellitus. Circulation 2008;117:2785-92.

[10] Tu AY, Albers JJ. Glucose regulates the transcription of human genes relevant to HDL metabolism. Diabetes 2001;50:1851-6.

[11] Silver DL, Jiang XC, Arai T, Bruce C, Tall AR. Receptors and lipid transfer proteins in HDL metabolism. Ann NY Acad Sci 2000;902:103-11.

[12] Packard CJ, Shepherd J. Lipoprotein heterogeneity and apolipoprotein B metabolism. Arterioscler Thromb Vasc Biol 1997;17:3542-56.

[13] Sakai T, Kamanna VS, Kashyap ML. Niacin, but not gemfibrozil, selectively increase Lp-A1, a cardioprotective subfraction of HDL, in patients with low HDL cholesterol. Arterioscler Thromb Vasc Biol 2001;21:1783-9.

[14] Rubic T, Trottmann M, Lorentz R. Stimulation of CD36 and the key effector of reverse cholesterol transport ATP-binding cassette A1 in monocytoid cells by niacin. Biochem Pharmacol 2004;67:411-9.

[15] Ganji SH, Kammanna VS, Kashyap ML. Niacin and cholesterol: role in cardiovascular disease. J Nutr Biochem 2003;14:298-305.

[16] Van J, Pan J, Charles MA, Krauss R, Wong N, Wu X. Atherogenic lipid phenotype in a general group of subjects. Arch Pathol Lab Med 2007;131:1679-85.

[17] Pan J, Van JT, Chan E, Kesala RL, Lin M, Charles MA. Extended-release niacin treatment of the atherogenic lipid profile and lipoprotein (a) in diabetes. Metabolism 2002;151:1120-7.

[18] O'Connor PM, Naya-Vigne JM, Duchateau PN, Ishida BY, Mazur M, Schoenhaus SA, et al. Measurement of prebeta-1 HDL in human plasma by an ultrafiltration-isotope dilution technique. Anal Biochem 1997;251:234-40.

[19] Hosseini SS, Bibler I, Charles MA. The narrow therapeutic window of glycated hemoglobin and assay variability. Metabolism 1999;48: 1498-502.

[20] O'Connor PM, Zysow BR, Schoenhaus SA, Ishida BY, Kunitake ST, Naya-Vigne JM, et al. Prebeta-1 HDL in plasma of normolipidemic individuals: influences of plasma lipoproteins, age, gender. J Lipid Res 1998;39:670-8.

[21] Miida T, Ozaki K, Murakami T, Kashiwa T, Yamdera T, Tsuda T, et al. Preβ1–high-density lipoprotein (preβ1-HDL) concentration can change with low-density lipoprotein-cholesterol (LDL-C) concentration independent of cholesteryl ester transfer protein (CETP). Clin Chim Acta 2000;292:69-80.

[22] Fievet C, Theret N, Shojaee N, Duchateau P, Castro G, Ailhaud G, et al. Apolipoprotein A-I containing particles and reverse cholesterol transport in IDDM. Diabetes 1992;41(Suppl 2):81-5.

[23] Peitzsch J, Julius U, Nitzsche S, Hanefeld M. In vivo evidence for increased apolipoprotein A-1 catabolism in subjects with impaired glucose tolerance. Diabetes 1998;47:1928-34.

[24] Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. Diabetologia 2003;46:733-49.

[25] Liadiki KN, Liu T, Xu S, Ishida BY, Duchateau PN, Krieger JP, et al. Binding of high density lipoprotein (HDL) and discoidal reconstituted HDL to the HDL receptor scavenger receptor Class B Type I. J Biol Chem 2000;275:21262-71.

[26] Mulya A, Lee JY, Gebre AK, Boudyguina EY, Chung SK, Smith TL, et al. Initial interaction of apoA-1 with ABCA1 impacts in vivo metabolic fate of nascent HDL. J Lipid Res 2008;49:2390-401.

[27] Van JT, Pan J, Wasty T, Chan E, Wu X, Charles MA. Comparison of extended-release niacin and atorvastatin monotherapies and combination treatment of the atherogenic lipid profile in diabetes mellitus. J Cardiol 2002;89:1306-8.

[28] Guerin M, Lassel TS, Le Goff W, Farnier M, Chapman MJ. Action of atorvastatin in combined hyperlipidemia: preferential reduction of cholesteryl ester transfer from HDL to VLDL1 particles. Arterioscler Thromb Vasc Biol 2000;20:189-97.