HHS Public Access

Author manuscript

Atherosclerosis. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Atherosclerosis. 2016 January ; 244: 93–100. doi:10.1016/j.atherosclerosis.2015.10.106.

Nuclear magnetic resonance-determined lipoprotein subclasses and carotid intima-media thickness in type 1 diabetes

Arpita Basu, PhD[1,*], **Alicia J. Jenkins, MD**[2,3,*], **Ying Zhang, MD, PhD**[4], **Julie A. Stoner, PhD**[4], **Richard L. Klein, PhD**[5,6], **Maria F. Lopes-Virella, MD, PhD**[5,6], **W. Timothy Garvey, MD**[7], **Timothy J. Lyons, MD**[2,8], and **The DCCT/EDIC Research Group**[9]

[1]Department of Nutritional Sciences, Oklahoma State University, Stillwater, Oklahoma

[2]Section of Endocrinology & Diabetes, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

[3]University of Sydney, NHMRC Clinical Trials Centre, Camperdown, Sydney, NSW, Australia

[4]Department of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

[5]Division of Endocrinology, Medical University of South Carolina, Charleston, South Carolina

[6]The Ralph H Johnson Veterans Affairs Medical Center, Charleston, South Carolina

[7]Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, Alabama

[8]Centre for Experimental Medicine, Queen's University of Belfast, Belfast, UK

Abstract

Background—Dyslipidemia has been linked to vascular complications of Type 1 diabetes (T1DM). We investigated the prospective associations of nuclear magnetic resonance-determined lipoprotein subclass profiles (NMR-LSP) and conventional lipid profiles with carotid intima-media thickness (IMT) in T1DM.

Methods—NMR-LSP and conventional lipids were measured in a subset of Diabetes Control and Complications Trial (DCCT) participants (n=455) at study entry ('baseline', 1983–89), and were related to carotid IMT determined by ultrasonography during the observational follow-up of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, at EDIC Year 12 (2004–2006). Associations were defined using multiple linear regression stratified by gender, and following adjustment for HbA1c, diabetes duration, body mass index, albuminuria, DCCT randomization group, smoking status, statin use, and ultrasound devices.

Correspondence: Timothy J Lyons, MD, FRCP, Centre for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University of Belfast, ICS Block A, Grosvenor Road, Belfast BT12 6BA, Northern Ireland, UK, Tel: 028 9063 2636; Fax: 028 9063 5012, t.lyons@qub.ac.uk.

[9]Box NDIC/EDIC, Bethesda, MD 20892

[*]contributed equally

DISCLOSURE STATEMENT: The authors have nothing to disclose.

Results—In men, significant positive associations were observed between some baseline NMR-subclasses of LDL (total IDL/LDL and large LDL) and common and/or internal carotid IMT, and between conventional total- and LDL-cholesterol and non-HDL-cholesterol and common carotid IMT, at EDIC Year 12; these persisted in adjusted analyses ($p<0.05$). Large LDL particles and conventional triglycerides were positively associated with common carotid IMT changes over 12 years ($p<0.05$). Inverse associations of mean HDL diameter and large HDL concentrations, and positive associations of small LDL with common and/or internal carotid IMT (all $p<0.05$) were found, but did not persist in adjusted analyses. No significant associations were observed in women.

Conclusion—NMR-LSP-derived LDL particles, in addition to conventional lipid profiles, may help in identifying men with T1DM at highest risk for vascular disease.

Keywords

Type 1 diabetes; LDL particles; non-HDL cholesterol; nuclear magnetic resonance-determined lipoprotein subclass profiles

1. Introduction

Dyslipidemia is an independent cardiovascular risk factor, and has been associated with vascular complications of type 1 diabetes (T1DM) [1]. Lipid and lipoprotein characteristics that are generally recognized as conferring cardiovascular risk, and that are routinely quantified by conventional lipid enzymology, include elevated total and low-density lipoprotein cholesterol (LDL-C), elevated triglycerides, and reduced high-density lipoprotein cholesterol (HDL-C) [2]. However, these conventional lipid/lipoprotein measures cannot detect more subtle forms of dyslipoproteinemia that have also been implicated in promoting the complications of diabetes [3]. Among techniques used to classify lipoprotein subclasses in greater detail, nuclear magnetic resonance (NMR) quantifies particles according to diameter, and from this information, molar concentrations of size/density-based subclasses are inferred, and these have been associated with glucose tolerance status and may predict vascular complications [4–6]. In our own work, NMR- determined Lipoprotein Subclass Profiles (NMR-LSP) characteristics of each major density-based lipoprotein class [LDL, very low-density lipoprotein (VLDL), and high density lipoprotein (HDL)], as well as particle diameters of LDL and HDL, have been significantly associated with vascular complications in cross-sectional studies of T1DM subjects [7–10].

Carotid intima-media thickness (IMT), a surrogate marker for atherosclerosis, is predictive of macrovascular events in the general population [11]. Consistent with their increased risk for cardiovascular disease (CVD), carotid IMT is increased in people with T1DM or Type 2 diabetes (T2DM) [12, 13]. Cross-sectional studies have reported significant associations between NMR-LSP and IMT in diabetic and non-diabetic populations, and predominantly involve LDL characteristics [4, 8, 14, 15]. Among reported studies, a few address prospective associations between NMR-LSP and advanced vascular complications in T1DM [16, 17], but do not include IMT as a primary outcome. The prospective report from the Finnish Diabetic Nephropathy Study Group, involving T1DM subjects with approximately nine years of follow-up, showed VLDL subclasses to be positively associated with

nephropathy and mortality, and large HDL to be inversely associated with mortality [16]. The Pittsburgh Epidemiology of Diabetes Complications Study also reported a significant protective association of large HDL particles, and showed positive associations of medium HDL and total VLDL particle concentrations with coronary artery disease in T1DM patients during 10 years follow-up [17]. On the other hand, in a cross-sectional report, no clear associations between the NMR-LSP and coronary artery calcification were observed in T1DM [18]. Thus, further investigation is needed to elucidate the associations of NMR-LSP with carotid IMT in T1DM patients.

The Diabetes Control and Complications Trial (DCCT) aimed to determine the effects of intensive diabetes therapy for blood glucose management on the development and progression of diabetic retinopathy [19]. The study cohort comprised young patients with T1DM who were free of overt CVD at enrollment in 1983–89. In 1994, the Epidemiology of Diabetes Interventions and Complications Trial (EDIC), a longitudinal observational phase of DCCT was initiated to assess the long-term effects of the DCCT intervention on cardiovascular and related complications [20]. Carotid IMT measurement were obtained at EDIC 'Years' 1 (1994–1996), 6 (1998–2000), and 12 (2004–2006). There has been considerable interest in identifying biomarkers for subclinical atherosclerosis in this cohort. Recent reports showed significant associations of composite, but not individual, biomarkers of inflammation and coagulation with IMT mainly at EDIC Year 12 [21]. We previously reported significant cross-sectional associations of NMR-derived LDL-subclasses and conventional LDL-C levels with IMT measured at EDIC Year 1, supporting the clinical utility of NMR-LSP in identifying patients at increased CVD risk [8]. The present prospective study is the first to examine, in T1DM patients, the relationship between detailed lipoprotein/lipid profiles and common and internal carotid IMT many years later.

2. Methods

2.1. Study subjects

The original DCCT cohort comprised 1,441 T1DM participants aged 13–39 years at study entry (1983–1989). They had no dyslipidemia or hypertension and were randomly assigned to conventional (n = 730) or intensive (n = 711) diabetes treatment [19]. In 1993, after a mean of 6.5 years treatment, the DCCT was terminated early because of highly significant beneficial effects of intensive therapy on diabetic retinopathy (the primary end-point) and other microvascular complications [19]. In 1994, EDIC, the observational phase of the study was initiated to assess the development of macrovascular disease, as well as the further progression of microvascular disease [20]. In 1996, a collaborative project between the Medical University of South Carolina (MUSC) and EDIC was implemented to identify markers and mechanisms for CVD in T1DM. Twenty-five of the 28 EDIC centers participated, and stored fasting sera from 580 DCCT subjects at baseline were available to our group for NMR-LSP analysis. Among the 580, 452 (244 men; 208 women) had available common carotid IMT measurements, and 445 (242 men; 203 women) had available internal carotid IMT measurements at EDIC Year 12. The study was approved by the Institutional Review Boards of MUSC, University of Oklahoma Health Sciences Center

(OUHSC), and all participating DCCT/EDIC centers, and written informed consent was obtained from all subjects.

2.2. Ultrasonography and image analysis

Common and internal carotid IMT measurements in EDIC have previously been described in detail [22]. In the current sub-study, we examined the prospective associations between lipoprotein profiles at DCCT entry (1983–89) and common and internal carotid IMT at EDIC Year 12, as well as IMT change from EDIC Year 1 to Year 12. Reliability measures for IMT readers at EDIC Years 1, 6, and 12 have been reported previously. For common carotid IMT, the primary reader had an intra-reader coefficient of reliability of >0.93, and the inter-reader reliability was >0.81. The coefficients were similar for the internal carotid IMT measures (>0.93 and >0.90, respectively) [23].

2.3. NMR Lipoprotein Subclass Analysis

Stored baseline DCCT serum samples were shipped to MUSC, maintained at −70°C, and subsequently sent for NMR analysis. NMR-LSP was determined in first-thaw serum specimens (250 μL) using a 400-MHz proton NMR analyzer at LipoScience Inc. (Raleigh, NC, USA) as described [24]. Lipoprotein subclasses were expressed as molar particle concentrations and defined by particle diameter: VLDL subclasses (large: 60–200 nm; medium: 35–59 nm; small: 27–34nm), intermediate density lipoprotein (IDL) (23–37nm), LDL subclasses (large: 21.3–23 nm; small: 18.3–21.2 nm), HDL subclasses (large: 8.9–13 nm; medium: 8.3–8.8 nm; small: 7.3–8.2 nm). Average VLDL, LDL, and HDL particle sizes (nm) were determined by weighting the relative mass percentage of each subclass by its diameter.

2.4. DCCT baseline conventional lipid profiles, HbA_{1c}, and other clinical measurements

Total cholesterol, triglyceride, and HDL-C levels were determined using previously reported methods [7]. LDL-C was estimated according to the Friedewald equation. HbA_{1c} was measured by high-performance ion exchange liquid chromatography [25].

2.5. Statistical analysis

Common and internal carotid IMT, conventional lipids, lipoprotein subclass measures, and clinical and demographic factors measured on a ratio scale at DCCT baseline were analyzed as continuous variables and are presented as means ± standard deviations according to gender. For those variables with skewed distribution (diabetes duration, urinary albumin excretion rate [AER], triglyceride, VLDL subclasses [large, medium, small and total]), data were summarized as medians and interquartile ranges. Student *t* tests were used to compare means for variables with normal distributions between men and women. The Wilcoxon rank sum test was used to compare median values between independent groups for variables with a skewed distribution. Proportions of smoking (status at DCCT baseline visit) were compared using a χ^2 test between men and women.

Two sets of multiple regression analyses were performed to examine correlations of the fifteen NMR-derived parameters and conventional lipid profiles at DCCT baseline with the two dependent variables: common and internal carotid IMT at EDIC Year 12, stratified by

gender. In addition, we analyzed IMT changes over 12 years (EDIC Year 12 minus Year 1) and their associations with NMR-LSP and conventional lipids using linear regression. We also conducted analyses combining data from men and women, to define the role of gender in the adjusted multiple regression model. Each lipoprotein/lipid measure was included as an independent variable in the linear model simultaneously with a fixed group of covariates that were measured at DCCT baseline: diabetes duration, smoking (yes/no), DCCT treatment group, body mass index (BMI), AER, and HbA_{1c}, statin use, and ultrasound imaging device. Univariate analyses were also performed without adjustment for these standard factors. Two-tailed $p < 0.05$ was considered to be statistically significant. Data were analyzed using SAS/STAT software (Version 9.2; SAS Institute Inc., Cary, NC).

3. Results

Table 1 summarizes the clinical characteristics of the T1DM participants (n=455) in the present study at DCCT entry (1983–89), categorized by gender. In men compared with women, systolic and diastolic blood pressures were significantly higher, and HbA1c was significantly lower. Measures of conventional lipid profiles, except LDL-C and non-HDL-C, and NMR-determined lipoprotein subclasses, except particle concentrations of small VLDL and total IDL/LDL, were significantly different between men and women at baseline. As shown in Supplemental Figure 1, at EDIC Year 12, common and internal carotid IMT were significantly greater in men than in women; and as summarized in Supplemental Table 1, the clinical characteristics of the study sub-set did not differ from those of the remaining (non-participating) DCCT subjects at study entry. The median follow-up time from study entry to EDIC Year 12 was 19 years (interquartile range: 18 – 21 years).

While no participants took statins DCCT study entry, approximately 41% in the intensive group and 37% in the conventional treatment group reported statin use at EDIC Year 12, albeit only for a short time. The overall median duration of statin use at EDIC Year 12 was 0 years with an interquartile range of 0 to 2 years. In the reported regression analyses, we adjusted for statin use at any time during the study.

Table 2 summarizes the associations of both NMR-LSP and conventional lipid profiles at DCCT baseline with common carotid IMT at EDIC Year 12, with participants stratified by gender. Unadjusted analyses of lipoprotein subclasses in men revealed significant positive associations of common carotid IMT with LDL subclasses (total IDL/LDL, large and small particles) (all $P<0.05$). When defined by diameter, only HDL (not LDL or VLDL) was associated (inversely) with common carotid IMT ($P<0.01$). Among conventional lipid profiles, unadjusted analyses revealed significant associations with LDL-, non-HDL- and total cholesterol, and triglyceride ($P<0.05$), and all but triglyceride persisted in the multivariate analysis. No significant associations were noted for HDL-C. No significant associations were observed in women. In adjusted analyses, LDL particle concentrations (total IDL/LDL and large LDL; both $P\leq0.01$), and conventional total, LDL-C and non-HDL-C (all $P<0.05$) remained associated with common carotid IMT, but in men only.

Table 3 summarizes the associations between lipoprotein measures and internal carotid IMT. In men, unadjusted analyses of lipoprotein subclasses revealed significant positive

associations of total IDL/LDL and small LDL particles, and an inverse association of large HDL particles, with internal carotid IMT (all P≤0.01). No significant associations were observed with VLDL-subclasses. When defined by diameter, only HDL size was inversely associated with internal carotid IMT (P<0.01). No associations were observed in women. Among conventional lipid profile measures, in men, unadjusted analyses showed LDL-, non-HDL- and total cholesterol and triglyceride to be significantly associated with internal carotid IMT (P<0.05), while HDL-C, though inversely associated, did not reach significance. Again, no associations at all were observed in women. In adjusted analyses in men, particle concentrations of total IDL/LDL remained significantly associated with internal carotid artery (P<0.05), while no significant associations were observed for VLDL- or HDL-subclasses, or for conventional lipid profiles. In general, in men, total IDL/LDL particles were positively associated with both common and internal IMT in unadjusted and adjusted analyses at EDIC Year 12, and this was also the case at EDIC Years 1 & 6 (Tables 1 & 2, Ref. [26]). No associations were noted in women.

The 12-year 'IMT change data' (IMT at EDIC Year 12 minus Year 1) revealed significant positive associations of NMR-derived large LDL particles and conventional triglycerides with the change in common carotid IMT, although only in men (P<0.05; Table 4), and these persisted in adjusted analyses. In unadjusted analyses, the 12-year change in internal carotid IMT was significantly associated with total IDL/LDL, conventional triglycerides and non-HDL-C, and inversely with large HDL particle concentrations, again only in men (P<0.05; Table 5). No such associations of lipoproteins with the 12 year change in IMT were observed in women.

In unadjusted analyses combining men and women (Supplemental Table 2) associations of total IDL/LDL (P<0.01) and small LDL (P≤0.01) particle concentrations with both common and internal carotid IMT were found, as were inverse associations with large HDL particle concentrations and HDL particle size. In adjusted models, total IDL/LDL and large LDL particles were associated with common, but not internal, carotid IMT (P≤0.01). No associations were observed between conventional lipid profiles and common carotid IMT after adjustment, but significant positive associations with triglycerides were noted in case of internal carotid IMT. To address the issue of stability of lipoprotein measures, we examined correlations of NMR-derived total IDL/LDL particle concentrations at DCCT baseline vs. EDIC years 2003–2006 (the latter being approximately contemporaneous with the EDIC 'Year 12' IMT measurements) and found significant correlations between the two time points (Supplemental Table 3).

4. Discussion

In our prospective study of a sub-set of the DCCT/EDIC cohort, both NMR-LSP and conventional lipid profiles at study entry (1983–89), in young men with T1DM, were associated with common and internal carotid IMT measured approximately 19 years later. In these men, we observed significant positive associations of NMR-derived concentrations of total IDL/LDL and large LDL particles with common and/or internal carotid IMT, and of conventional total, LDL- and non-HDL-C with common carotid IMT, in multiple regression analyses adjusted for DCCT randomization groups, diabetes duration, HbA1c, AER, BMI,

smoking status, statin use and ultrasound imaging devices. Consistent conclusions were drawn from the analyses of IMT progression *between* EDIC Years 1 and 12, and IMT *at* EDIC Years 1 and 6 (see Ref. [26]). The additional predictive value of NMR-LSP is consistent with results from previous studies revealing stronger associations of NMR-LSP than conventional lipids with insulin resistance and CVD [6, 27]. The clinical utility of LDL particle concentration has been emphasized by the National Lipid Association (NLA), and in the presence of diabetes or the metabolic syndrome, may be more predictive than LDL-C of atherosclerotic CVD [28].

Interestingly, no associations between measures of either NMR-derived or conventional lipoprotein/lipid profiles and IMT were observed in women. This could be explained by the cardio-protective effects of estrogen related to lipid metabolism [29], smaller IMT in women than in men, and/or the small sample size of our cohort. Our gender-specific findings are consistent with the previously reported DCCT/EDIC observations showing significantly higher internal carotid IMT in diabetic men, but similar IMT values in women, when compared to age-matched non-diabetic controls [30], and more atherogenic lipoprotein profiles in males vs. females following DCCT completion [7]. Furthermore, differences in blood pressure could also contribute; systolic and diastolic blood pressure were significantly higher in men vs. women at DCCT baseline. Recent genetic studies also reveal multiple gender-specific determinants that may explain greater IMT in men vs. women [31].

Cross-sectional studies of people with T2DM, using different means to assess LDL subclasses, have demonstrated associations of small LDL, IDL, and LDL particle size with cardiovascular risk and IMT [32–35]. Other studies of people at high risk for CVD, such as the Monitored Atherosclerosis Regression Study (MARS) [36] and the National Heart, Lung, and Blood Institute (NHLBI) Coronary Intervention Study [37], reached similar conclusions. These studies are consistent with the prospective associations between LDL-related subclasses and IMT that we now report in T1DM.

Among observational studies addressing the role of lipids/lipoproteins in macrovascular complications in T1DM [8, 17, 18, 38], only a few have examined associations with carotid IMT [8, 38]. We previously reported cross-sectional associations of NMR-determined LDL subclasses, conventional LDL-C, and apolipoprotein B (ApoB) levels with internal carotid IMT in both men and women; while for common carotid IMT, these associations were observed only in men [8]. Our current prospective findings are consistent: we found positive associations of LDL characteristics at DCCT baseline (NMR-based large LDL and total IDL/LDL particles; conventional LDL-C) with carotid IMT at EDIC Year 12, again only in men. Thus, elevated baseline NMR-determined IDL/LDL particles in young men with T1DM may be associated with increased CVD risk even after many years of improved glycemic control. Even during the observational phase (EDIC), both the prior intensive and conventional diabetes treatment groups of the DCCT had better glycemic control than at DCCT entry [20].

HDL-C levels tend to be similar or increased in T1DM patients compared to non-diabetic subjects [39, 40], but may also exhibit qualitative differences, especially affecting large HDL particles, that might contribute to promotion of subclinical atherosclerosis in T1DM [39]. In

the present study, we observed significant inverse associations of both large HDL particle concentrations and HDL particle diameter (at DCCT baseline) with carotid IMT (at EDIC Year 12); but again only in men and in univariate analysis. These findings are broadly consistent with our previously reported cross-sectional data reporting non-significant associations between NMR-based HDL subclasses and carotid IMT examined at EDIC Year 1; but in that case involving both men and women in multivariate analyses [8]. Our present findings also conform to a previous report of significant associations between IMT progression, examined between EDIC Years 1 and 6, and conventional lipid profiles (ratio of LDL- and HDL-C, although not HDL-C *per se*): however, in that study, lipoprotein subclasses were not measured [22]. Another small cross-sectional study of young participants with T1DM found that conventional HDL-C was inversely associated with carotid IMT, but again did not measure subclasses [38]. In studies of patients with T2DM or advanced CVD, conventional HDL-C and/or NMR-based HDL particle size have been significantly correlated with carotid IMT in some [33, 41] but not in others [32, 34, 36]. Thus, there is a paucity of data on the associations of HDL subclasses and IMT in T1DM cohorts. Our data suggest some protective associations, but only in men and in univariate analyses.

Triglycerides and NMR-based VLDL subclasses have been reported as strong predictors of coronary artery disease in participants with T1DM [17] as well as in non-diabetic men with advanced CVD [42]. Triglyceride-rich lipoproteins have been shown to be atherogenic [43], consistent with our observation of a univariate positive association between conventional triglyceride levels and both common and internal carotid IMT in men. Our previous cross-sectional data revealed significant associations in multivariate analyses between NMR-based large VLDL subclass and carotid IMT, again in men only, and using a larger sample size [8]. Thus, in comparison to the previously reported prospective studies [17, 42, 43], the lack of significance in associations of VLDL subclasses with carotid IMT in the present study may be indicative of a role for these lipoproteins in the more advanced lesions, detected by coronary angiography, rather than in subclinical atherosclerosis assessed by carotid IMT.

The present study does not address other qualitative characteristics of lipoprotein particles that may be important in the promotion of diabetic vascular complications. Modification of particles by glycation and/or oxidation may enhance atherogenicity [44, 45], as may variations in their apolipoprotein constituents [46]. Also, formation of immune complexes containing oxidized LDL may be important: we recently reported prospective associations between levels of LDL immune complexes at DCCT baseline with IMT measured years later during EDIC [47]. These considerations emphasize the potential importance of qualitative lipoprotein characteristics as both markers and mechanisms of disease: none of these characteristics can be discerned in a conventional lipid profile.

Our study limitations include the absence of non-diabetic controls, the small sample size of our cohort, and the assessment of lipid and NMR-LSP at one time point only. Also, we did not analyze other lipid/lipoprotein measures, such as individual serum apolipoproteins, lipoprotein(a) [Lp(a)], extent of LDL glycation or oxidation, or levels of modified lipids in immune complexes, all of which might provide further details on the associations with IMT in T1DM participants. Its strengths include the rigorous follow-up of the DCCT/EDIC

cohort, and the fact that it is the first prospective study to assess lipoprotein subclass associations with carotid IMT. Our exploratory analysis also supports the long-term stability of NMR-based total IDL/LDL particle concentrations between two DCCT/EDIC time points (determined approximately 19 years apart).

In conclusion, our present analyses reveal significant prospective associations of NMR-determined concentrations of total IDL/LDL particles and large LDL, as well as conventional cholesterol levels (total, LDL-C and non-HDL-C) at DCCT study entry, with carotid IMT 19 years later at EDIC Year 12, but only in men. Similar observations were noted in pooled analyses combining men and women. Atherosclerosis is a chronic condition with gradual and silent progression, and early detection and management of high-risk lipid/lipoprotein profiles, including those revealed by advanced lipid/lipoprotein testing, is important for the management of patients with type 1 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project was funded supported by grants from the National Institute of Health (R01DK080043) and the American Diabetes Association (7-12-CT-46).

DCCT/EDIC has been supported by U01 Cooperative Agreement grants (1982–93, 2011–2016), and contracts (1982–2011) with the Division of Diabetes Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Disease, and through support by the National Eye Institute, the National Institute of Neurologic Disorders and Stroke, the Genetic Clinical Research Centers Program (1993–2007), and Clinical Translational Science Center Program (2006-present), Bethesda, Maryland, USA. A complete list of participants in the DCCT/EDIC research group can be found in New England Journal of Medicine, 2011;365:2366-2376.

Industry contributors have had no role in the DCCT/EDIC study but have provided free or discounted supplies or equipment to support participants' adherence to the study: Abbott Diabetes Care (Alameda, CA), Animas (Westchester, PA), Bayer Diabetes Care (North America Headquarters, Tarrytown NY) Becton Dickinson (Franklin Lakes, NJ), CanAm (Atlanta, GA), Eli Lilly (Indianapolis, IN), Lifescan (Milpitas, CA), Medtronic Diabetes Minneapolis, MI), Omron (Shelton CT), OmniPod® Insulin Management System Bedford, MA, Roche Diabetes Care (Indianapolis, IN), and Sanofi-Aventis (Bridgewater NJ)

No other potential conflicts of interest relevant to this article were reported. The authors would like to thank John W. Baynes, PhD and Sue Thorpe, PhD, for helpful discussions.

A.B., A.J.J., Y.Z., and J.A.S. analyzed data, wrote, reviewed and edited the manuscript. R.L.K., M.F. L-V. and W.T.G. reviewed and edited the manuscript. T.J.L. wrote, reviewed and edited the manuscript. T.J.L. is the guarantor of this work.

References

1. Maser RE, Wolfson SK Jr, Ellis D, et al. Cardiovascular disease and arterial calcification in insulin-dependent diabetes mellitus: interrelations and risk factor profiles. Pittsburgh Epidemiology of Diabetes Complications Study-V. Arterioscler Thromb. 1991; 11:958–965. [PubMed: 2065046]
2. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2010; 122:e584–636. [PubMed: 21098428]

3. Al-Shahrouri HZ, Ramirez P, Fanti P, Abboud H, Lorenzo C, Haffner S. NMR identifies atherogenic lipoprotein abnormalities in early diabetic nephropathy that are unrecognized by conventional analysis. Clin Nephrol. 2010; 73:180–189. [PubMed: 20178716]
4. Mora S, Szklo M, Otvos JD, et al. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2007; 192:211–217. [PubMed: 16765964]
5. Wang J, Stancakova A, Soininen P, et al. Lipoprotein subclass profiles in individuals with varying degrees of glucose tolerance: a population-based study of 9399 Finnish men. J Intern Med. 2012; 272:562–572. [PubMed: 22650159]
6. Garvey WT, Kwon S, Zheng D, et al. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. Diabetes. 2003; 52:453–462. [PubMed: 12540621]
7. Jenkins AJ, Lyons TJ, Zheng D, et al. Serum lipoproteins in the diabetes control and complications trial/epidemiology of diabetes intervention and complications cohort: associations with gender and glycemia. Diabetes Care. 2003; 26:810–818. [PubMed: 12610042]
8. Lyons TJ, Jenkins AJ, Zheng D, et al. Nuclear magnetic resonance-determined lipoprotein subclass profile in the DCCT/EDIC cohort: associations with carotid intima-media thickness. Diabet Med. 2006; 23:955–966. [PubMed: 16922701]
9. Jenkins AJ, Lyons TJ, Zheng D, et al. Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. Kidney Int. 2003; 64:817–828. [PubMed: 12911531]
10. Lyons TJ, Jenkins AJ, Zheng D, et al. Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort. Invest Ophthalmol Vis Sci. 2004; 45:910–918. [PubMed: 14985310]
11. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. 1999; 340:14–22. [PubMed: 9878640]
12. Bonora E, Tessari R, Micciolo R, et al. Intimal-medial thickness of the carotid artery in nondiabetic and NIDDM patients. Relationship with insulin resistance. Diabetes Care. 1997; 20:627–631. [PubMed: 9096992]
13. Yamasaki Y, Kawamori R, Matsushima H, et al. Atherosclerosis in carotid artery of young IDDM patients monitored by ultrasound high-resolution B-mode imaging. Diabetes. 1994; 43:634–639. [PubMed: 8168638]
14. Jarauta E, Mateo-Gallego R, Gilabert R, et al. Carotid atherosclerosis and lipoprotein particle subclasses in familial hypercholesterolaemia and familial combined hyperlipidaemia. Nutr Metab Cardiovasc Dis. 2012; 22:591–597. [PubMed: 21196102]
15. Masulli M, Patti L, Riccardi G, et al. Relation among lipoprotein subfractions and carotid atherosclerosis in Alaskan Eskimos (from the GOCADAN Study). Am J Cardiol. 2009; 104:1516–1521. [PubMed: 19932785]
16. Makinen VP, Soininen P, Kangas AJ, et al. Triglyceride-cholesterol imbalance across lipoprotein subclasses predicts diabetic kidney disease and mortality in type 1 diabetes: the FinnDiane Study. J Intern Med. 2013; 273:383–395. [PubMed: 23279644]
17. Soedamah-Muthu SS, Chang YF, Otvos J, Evans RW, Orchard TJ. Lipoprotein subclass measurements by nuclear magnetic resonance spectroscopy improve the prediction of coronary artery disease in Type 1 diabetes. A prospective report from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetologia. 2003; 46:674–682. [PubMed: 12743701]
18. Colhoun HM, Otvos JD, Rubens MB, Taskinen MR, Underwood SR, Fuller JH. Lipoprotein subclasses and particle sizes and their relationship with coronary artery calcification in men and women with and without type 1 diabetes. Diabetes. 2002; 51:1949–1956. [PubMed: 12031985]
19. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329:977–986. [PubMed: 8366922]
20. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care. 1999; 22:99–111. [PubMed: 10333910]

21. Hunt KJ, Baker NL, Cleary PA, Klein R, Virella G, Lopes-Virella MF. Longitudinal Association Between Endothelial Dysfunction, Inflammation, and Clotting Biomarkers With Subclinical Atherosclerosis in Type 1 Diabetes: An Evaluation of the DCCT/EDIC Cohort. Diabetes Care. 2015; 38:1281–1289. [PubMed: 25852210]
22. Nathan DM, Lachin J, Cleary P, et al. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med. 2003; 348:2294–2303. [PubMed: 12788993]
23. Polak JF, Backlund JY, Cleary PA, et al. Progression of carotid artery intima-media thickness during 12 years in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Diabetes. 2011; 60:607–613. [PubMed: 21270271]
24. Otvos JD, Jeyarajah EJ, Bennett DW. Quantification of plasma lipoproteins by proton nuclear magnetic resonance spectroscopy. Clin Chem. 1991; 37:377–386. [PubMed: 2004444]
25. The DCCT Research Group. Feasibility of centralized measurements of glycated hemoglobin in the Diabetes Control and Complications Trial: a multicenter study. Clin Chem. 1987; 33:2267–2271. [PubMed: 3319291]
26. Basu A, Jenkins AJ, Zhang Y, et al. The DCCT/EDIC Research Group. Carotid intima-media thickness and lipoprotein subclasses in type 1 diabetes: results from the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC). Data in Brief. 2015 submitted.
27. Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. Circulation. 2013; 128:1189–1197. [PubMed: 24002795]
28. Bays HE, Jones PH, Brown WV, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2015. J Clin Lipidol. 2014; 8:S1–36. [PubMed: 25523435]
29. Lobo RA. Estrogen and cardiovascular disease. Ann N Y Acad Sci. 1990; 592:286–294. discussion 334–245. [PubMed: 2197947]
30. Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Effect of intensive diabetes treatment on carotid artery wall thickness in the epidemiology of diabetes interventions and complications. Diabetes. 1999; 48:383–390. [PubMed: 10334318]
31. Dong C, Della-Morte D, Beecham A, et al. Genetic variants in LEKR1 and GALNT10 modulate sex-difference in carotid intima-media thickness: a genome-wide interaction study. Atherosclerosis. 2015; 240:462–467. [PubMed: 25898001]
32. Inukai T, Yamamoto R, Suetsugu M, et al. Small low-density lipoprotein and small low-density lipoprotein/total low-density lipoprotein are closely associated with intima-media thickness of the carotid artery in Type 2 diabetic patients. J Diabetes Complications. 2005; 19:269–275. [PubMed: 16112502]
33. Hayashi Y, Okumura K, Matsui H, et al. Impact of low-density lipoprotein particle size on carotid intima-media thickness in patients with type 2 diabetes mellitus. Metabolism. 2007; 56:608–613. [PubMed: 17445534]
34. Berneis K, Jeanneret C, Muser J, Felix B, Miserez AR. Low-density lipoprotein size and subclasses are markers of clinically apparent and non-apparent atherosclerosis in type 2 diabetes. Metabolism. 2005; 54:227–234. [PubMed: 15690318]
35. Gerber PA, Thalhammer C, Schmied C, et al. Small, dense LDL particles predict changes in intima media thickness and insulin resistance in men with type 2 diabetes and prediabetes--a prospective cohort study. PLoS One. 2013; 8:e72763. [PubMed: 23951331]
36. Hodis HN, Mack WJ, Dunn M, Liu C, Selzer RH, Krauss RM. Intermediate- density lipoproteins and progression of carotid arterial wall intima-media thickness. Circulation. 1997; 95:2022–2026. [PubMed: 9133510]
37. Krauss RM, Lindgren FT, Williams PT, et al. Intermediate-density lipoproteins and progression of coronary artery disease in hypercholesterolaemic men. Lancet. 1987; 2:62–66. [PubMed: 2885572]
38. Pinto CS, Lana JM, Gabbay MA, de Sa JR, Dib SA. HDL cholesterol levels and weight are the main determinants of subclinical atherosclerosis in the young with type 1 diabetes and suitable glycaemic control. Diab Vasc Dis Res. 2014; 11:125–128. [PubMed: 24553254]

39. Valabhji J, McColl AJ, Schachter M, Dhanjil S, Richmond W, Elkeles RS. High- density lipoprotein composition and paraoxonase activity in Type I diabetes. Clin Sci (Lond). 2001; 101:659–670. [PubMed: 11724654]
40. Feitosa AC, Feitosa-Filho GS, Freitas FR, Wajchenberg BL, Maranhao RC. Lipoprotein metabolism in patients with type 1 diabetes under intensive insulin treatment. Lipids Health Dis. 2013; 12:15. [PubMed: 23398881]
41. Mackey RH, Greenland P, Goff DC Jr, Lloyd-Jones D, Sibley CT, Mora S. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (multi-ethnic study of atherosclerosis). J Am Coll Cardiol. 2012; 60:508–516. [PubMed: 22796256]
42. Freedman DS, Otvos JD, Jeyarajah EJ, Barboriak JJ, Anderson AJ, Walker JA. Relation of lipoprotein subclasses as measured by proton nuclear magnetic resonance spectroscopy to coronary artery disease. Arterioscler Thromb Vasc Biol. 1998; 18:1046–1053. [PubMed: 9672064]
43. Havel RJ. Role of triglyceride-rich lipoproteins in progression of atherosclerosis. Circulation. 1990; 81:694–696. [PubMed: 2297871]
44. Isoda K, Folco E, Marwali MR, Ohsuzu F, Libby P. Glycated LDL increases monocyte CC chemokine receptor 2 expression and monocyte chemoattractant protein-1-mediated chemotaxis. Atherosclerosis. 2008; 198:307–312. [PubMed: 18164016]
45. Witztum JL, Steinberg D. Role of oxidized low density lipoprotein in atherogenesis. J Clin Invest. 1991; 88:1785–1792. [PubMed: 1752940]
46. Rabbani N, Chittari MV, Bodmer CW, Zehnder D, Ceriello A, Thornalley PJ. Increased glycation and oxidative damage to apolipoprotein B100 of LDL cholesterol in patients with type 2 diabetes and effect of metformin. Diabetes. 2010; 59:1038–1045. [PubMed: 20068133]
47. Lopes-Virella MF, Hunt KJ, Baker NL, Lachin J, Nathan DM, Virella G. Levels of oxidized LDL and advanced glycation end products-modified LDL in circulating immune complexes are strongly associated with increased levels of carotid intima-media thickness and its progression in type 1 diabetes. Diabetes. 2011; 60:582–589. [PubMed: 20980456]

Highlights

- NMR-derived and conventional lipid profiles were correlated with carotid IMT
- Analyses were conducted in a DCCT/EDIC sub study, (n=455)
- Lipids were measured at baseline and correlated with IMT about 19 years later
- LDL subclasses (total IDL/LDL and large LDL) were positively associated with IMT in men
- Conventional total and LDL-cholesterol levels were positively associated with IMT in men
- No statistically significant associations were observed in women

Table 1

DCCT baseline characteristics (1983–89) of the reported sub-set of DCCT participants (n=455), according to gender

Characteristics	Men (n=246) (mean ± SD)*	Women (n=209) (mean ± SD)*	P†
Age (years)	28 ± 6.2	28 ± 7.0	0.70
Intensive treatment (%)	62.6	55.0	0.10
Duration of diabetes (years)	4.0 (2.1, 8.8)	3.9 (2.2, 9.3)	0.96
Current cigarette smoker (%)	23	20	0.43
Body-mass index (kg/m^2)	23.6 ± 2.5	23.2 ± 2.8	0.11
Blood pressure (mmHg)			
Systolic	118 ± 10	110 ± 11	**<0.0001**
Diastolic	75 ± 8	69 ± 9	**<0.0001**
Albumin excretion rate (mg/24hr)	9.4 (5.8, 15.8)	10.1 (5.8, 20.2)	0.32
Glomerular filtration rate (ml/minute)	125.6 ± 20.3	125.9 ± 18.3	0.91
Conventional lipids			
Total cholesterol (mg/dl)	174 ± 33	186 ± 31	**0.0002**
Triglyceride (mg/dl)	73 (55, 97)	67 (52, 87)	**0.03**
LDL cholesterol (mg/dl)	111 ± 29	114 ± 26	0.20
Non-HDL (mg/dl)	127.6 (32.7)	129.2 (29.7)	0.57
HDL cholesterol (mg/dl)	47 ± 11	57 ± 13	**<0.0001**
HbA_{1c} (%)	8.36 ± 1.40	8.80 ± 1.66	**0.0026**
NMR subclasses			
Total VLDL and chylomicrons (nmol/L)	49.0 (32.0, 69.0)	40.0 (29.0, 58.0)	**0.0011**
Large VLDL & chylomicrons (nmol/L)	1.8 (0.9, 3.3)	1.3 (0.7, 2.1)	**<0.0001**
Medium VLDL (nmol/L)	15.0 (9.0, 23.0)	11.0 (7.0, 16.0)	**<0.0001**
Small VLDL (nmol/L)	32.0 (16.0, 48.0)	30.0 (16.0, 43.0)	0.31
Total IDL/LDL (nmol/L)	993 ± 338	1015 ± 325	0.48
IDL (nmol/L)	195 ± 123	242 ± 129	**<0.0001**
Large LDL (nmol/L)	363 ± 248	491 ± 251	**<0.0001**
Small LDL (nmol/L)	435 ± 377	282 ± 326	**<0.0001**
Total HDL (μmol/L)	32.0 ± 5.0	34.0 ± 6.0	**0.0009**
Large HDL (μmol/L)	6.1 ± 2.8	8.2 ± 3.1	**<0.0001**
Medium HDL (μmol/L)	9.1 ± 4.8	11.0 ± 6.0	**0.003**
Small HDL (μmol/L)	17.0 ± 5.0	15.0 ± 6.0	**0.0002**
NMR particle diameter			
VLDL particle size (nm)	46.0 ± 6.0	45.0 ± 5.0	**0.023**
LDL particle size (nm)	21.0 ± 0.6	21.0 ± 0.5	**<0.0001**
HDL particle size (nm)	9.4 ± 0.5	9.7 ± 0.5	**<0.0001**

*If the distribution of a continuous variable is skewed, median and the interquartile range (Q_1, Q_3) are presented.

[†]Comparison between men and women: t test for difference in means, χ^2 test for difference in proportions, and Wilcoxon rank sum test for difference of continuous variables with skewed distributions. P values shown in bold if significant (<0.05).

Table 2

DCCT baseline lipoprotein profiles vs. common carotid IMT at EDIC year 12 (Standardized linear regression coefficients)

Variables	Men (n=244)				Women (n=208)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
NMR subclasses	Slope(SE)	P	Slope(SE)	P	Slope(SE)	P	Slope SE	P
Total VLDL and chylomicrons (nmol/L)	0.08 (0.06)	0.19	0.003 (0.06)	0.96	−0.03 (0.07)	0.71	−0.03 (0.08)	0.73
Large VLDL & chylomicrons (nmol/L)	0.05 (0.06)	0.39	−0.06 (0.06)	0.37	0.03 (0.07)	0.69	0.01 (0.08)	0.89
Medium VLDL (nmol/L)	−0.01 (0.06)	0.88	−0.06 (0.06)	0.26	−0.03 (0.08)	0.75	−0.02 (0.09)	0.85
Small VLDL (nmol/L)	0.11 (0.06)	0.09	0.05 (0.06)	0.43	−0.02 (0.07)	0.72	−0.03 (0.07)	0.72
Total IDL/LDL (nmol/L)	0.27 (0.06)	**<0.0001**	0.20 (0.06)	**0.001**	0.06 (0.07)	0.35	0.08 (0.07)	0.30
IDL (nmol/L)	0.01 (0.07)	0.91	−0.04 (0.06)	0.51	0.05 (0.07)	0.49	0.05 (0.07)	0.51
Large LDL (nmol/L)	0.17 (0.07)	**0.009**	0.16 (0.06)	**0.01**	0.0. (0.07)	0.67	0.04 (0.07)	0.59
Small LDL (nmol/L)	0.13 (0.06)	**0.03**	0.07 (0.06)	0.22	0.03 (0.07)	0.73	0.03 (0.08)	0.73
Total HDL (μmol/L)	0.01 (0.07)	0.89	−0.02 (0.07)	0.81	0.06 (0.06)	0.34	0.04 (0.06)	0.54
Large HDL (μmol/L)	−0.09 (0.07)	0.23	0.01 (0.07)	0.84	0.03 (0.07)	0.70	0.03 (0.07)	0.70
Medium HDL (μmol/L)	0.02 (0.08)	0.83	−0.02 (0.07)	0.76	0.02 (0.06)	0.67	0.01 (0.06)	0.90
Small HDL (μmol/L)	0.04 (0.07)	0.56	−0.005 (0.07)	0.94	0.02 (0.06)	0.70	0.02 (0.07)	0.73
NMR particle diameter								
VLDL particle size (nm)	−0.02 (0.06)	0.75	−0.07 (0.06)	0.28	0.07 (0.07)	0.32	0.05 (0.07)	0.47
LDL particle size (nm)	−0.005 (0.06)	0.94	0.02 (0.06)	0.76	0.01 (0.08)	0.90	0.01 (0.08)	0.92
HDL particle size (nm)	−0.13 (0.07)	**0.046**	−0.05 (0.06)	0.44	0.04 (0.07)	0.60	0.05 (0.08)	0.54
Conventional lipids								
Total cholesterol (mg/dl)	0.18 (0.06)	**0.0045**	0.13 (0.06)	**0.03**	0.05 (0.07)	0.47	0.06 (0.07)	0.40
Triglyceride (mg/dl)	0.14 (0.05)	**0.01**	0.05 (0.05)	0.32	−0.03 (0.09)	0.73	−0.06 (0.10)	0.54
LDL cholesterol (mg/dl)	0.17 (0.06)	**0.006**	0.13 (0.16)	**0.03**	0.03 (0.07)	0.68	0.04 (0.07)	0.54
Non-HDL cholesterol (mg/dl)	0.18 (0.06)	**0.0025**	0.12 (0.06)	**0.04**	0.02 (0.07)	0.78	0.03 (0.08)	0.68
HDL cholesterol (mg/dl)	−0.03 (0.08)	0.72	0.05 (0.07)	0.46	0.07 (0.06)	0.29	0.07 (0.07)	0.28

*Models were adjusted for DCCT randomization, albumin excretion rate, HbA_{1C}, diabetes duration, body mass index, and current smoking at DCCT baseline (1983–89). The regression models were also adjusted for statin use (any time during the DCCT baseline to EDIC year 12), ultrasound devices, and image readers at EDIC year 12.

P values in bold if significant (<0.05).

Table 3

DCCT baseline lipoprotein profiles vs. internal carotid IMT at EDIC year 12 (Standardized linear regression coefficients)

Variables	Men (n=242)				Women (n=203)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
NMR subclasses	Slope(SE)	P	Slope(SE)	P	Slope(SE)	P	Slope(SE)	P
Total VLDL and chylomicrons (nmol/L)	0.02 (0.07)	0.72	−0.04 (0.07)	0.52	0.06 (0.06)	0.33	0.08 (0.06)	0.22
Large VLDL & chylomicrons (nmol/L)	0.07 (0.07)	0.33	−0.02 (0.07)	0.81	0.02 (0.07)	0.73	0.03 (0.07)	0.67
Medium VLDL (nmol/L)	0.02 (0.07)	0.79	−0.04 (0.06)	0.55	0.07 (0.07)	0.30	0.11 (0.07)	0.12
Small VLDL (nmol/L)	0.02 (0.07)	0.83	−0.03 (0.07)	0.63	0.04 (0.06)	0.47	0.05 (0.06)	0.43
Total IDL/LDL (nmol/L)	0.26 (0.07)	**0.0001**	0.14 (0.07)	**0.038**	0.01 (0.06)	0.83	−0.01 (0.06)	0.82
IDL (nmol/L)	0.04 (0.07)	0.56	−0.03 (0.07)	0.68	0.03 (0.06)	0.55	0.05 (0.06)	0.37
Large LDL (nmol/L)	0.06 (0.07)	0.43	0.03 (0.07)	0.68	−0.03 (0.06)	0.57	−0.06 (0.06)	0.29
Small LDL (nmol/L)	0.18 (0.07)	**0.007**	0.11 (0.07)	0.10	0.03 (0.06)	0.68	0.01 (0.06)	0.84
Total HDL (µmol/L)	0.04 (0.08)	0.65	0.02 (0.07)	0.76	−0.05 (0.05)	0.37	−0.08 (0.05)	0.13
Large HDL (µmol/L)	−0.19 (0.08)	**0.01**	−0.11 (0.08)	0.16	−0.01 (0.06)	0.92	−0.001 (0.06)	0.99
Medium HDL (µmol/L)	0.07 (0.08)	0.43	0.07 (0.08)	0.38	−0.04 (0.05)	0.43	−0.06 (0.05)	0.19
Small HDL (µmol/L)	0.08 (0.08)	0.29	0.02 (0.07)	0.80	−0.002 (0.06)	0.98	−0.01 (0.06)	0.87
NMR particle diameter								
VLDL particle size (nm)	0.05 (0.07)	0.43	0.02 (0.07)	0.83	−0.03 (0.07)	0.66	0.02 (0.07)	0.72
LDL particle size (nm)	−0.07 (0.07)	0.31	−0.05 (0.07)	0.44	−0.04 (0.06)	0.52	−0.05 (0.06)	0.44
HDL particle size (nm)	−0.21 (0.07)	**0.004**	−0.14 (0.07)	0.06	0.04 (0.06)	0.54	0.07 (0.06)	0.24
Conventional lipids								
Total cholesterol (mg/dl)	0.19 (0.07)	**0.005**	0.08 (0.07)	0.24	0.04 (0.06)	0.53	0.02 (0.06)	0.75
Triglyceride (mg/dl)	0.18 (0.06)	**0.004**	0.10 (0.06)	0.11	0.11 (0.08)	0.17	0.14 (0.08)	0.11
LDL cholesterol (mg/dl)	0.20 (0.07)	**0.003**	0.08 (0.07)	0.23	0.02 (0.06)	0.78	−0.01 (0.06)	0.81
Non-HDL cholesterol (mg/dl)	0.22 (0.07)	**0.001**	0.09 (0.07)	0.19	0.04 (0.06)	0.55	0.01 (0.06)	0.87
HDL cholesterol (mg/dl)	−0.11 (0.08)	0.21	−0.02 (0.08)	0.84	0.01 (0.06)	0.89	0.02 (0.06)	0.70

*Models were adjusted for DCCT randomization, albumin excretion rate, HbA_{1C}, diabetes duration, body mass index, and current smoking at DCCT baseline (1983–89). The regression models were also adjusted for statin use (any time during the DCCT baseline to EDIC year 12), ultrasound devices, and image readers at EDIC year 12.

P values in bold if significant (<0.05).

Table 4

DCCT baseline lipoprotein profiles vs. common carotid IMT change from EDIC year 1 to year 12 (year12–year1) (Standardized linear regression coefficients)

Variables	Men (n=244)				Women (n=208)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
NMR subclasses	Slope(SE)	P	Slope(SE)	P	Slope(SE)	P	Slope SE	P
Total VLDL and chylomicrons (nmol/L)	0.03 (0.05)	0.55	−0.02 (0.05)	0.67	0.02 (0.06)	0.76	0.01 (0.06)	0.87
Large VLDL & chylomicrons (nmol/L)	0.05 (0.05)	0.38	0.05 (0.05)	0.34	−0.03 (0.06)	0.62	−0.01 (0.06)	0.85
Medium VLDL (nmol/L)	0.03 (0.05)	0.52	0.03 (0.05)	0.60	−0.05 (0.07)	0.47	−0.01 (0.07)	0.90
Small VLDL (nmol/L)	0.02 (0.05)	0.74	−0.05 (0.05)	0.35	0.04 (0.06)	0.46	0.02 (0.06)	0.79
Total IDL/LDL (nmol/L)	0.08 (0.05)	0.13	0.08 (0.05)	0.14	−0.04 (0.06)	0.44	−0.02 (0.06)	0.78
IDL (nmol/L)	−0.02 (0.06)	0.76	0.003 (0.05)	0.95	−0.06 (0.06)	0.32	−0.03 (0.06)	0.54
Large LDL (nmol/L)	0.12 (0.06)	**0.039**	0.12 (0.05)	**0.03**	−0.08 (0.06)	0.26	−0.08 (0.06)	0.19
Small LDL (nmol/L)	0.01 (0.05)	0.90	−0.01 (0.05)	0.85	0.03 (0.06)	0.62	0.07 (0.07)	0.32
Total HDL (μmol/L)	0.02 (0.06)	0.70	0.03 (0.06)	0.57	−0.03 (0.05)	0.52	−0.06 (0.05)	0.24
Large HDL (μmol/L)	0.03 (0.06)	0.60	0.10 (0.06)	0.10	−0.04 (0.06)	0.52	−0.07 (0.06)	0.25
Medium HDL (μmol/L)	0.12 (0.06)	0.06	0.10 (0.06)	0.11	−0.01 (0.05)	0.79	−0.01 (0.05)	0.79
Small HDL (μmol/L)	−0.09 (0.06)	0.11	−0.10 (0.06)	0.08	−0.002 (0.06)	0.97	−0.02 (0.05)	0.68
NMR particle diameter								
VLDL particle size (nm)	0.06 (0.05)	0.30	0.09 (0.05)	0.08	0.002 (0.06)	0.98	0.004 (0.06)	0.95
LDL particle size (nm)	0.05 (0.05)	0.36	0.06 (0.05)	0.25	−0.01 (0.07)	0.83	−0.03 (0.07)	0.68
HDL particle size (nm)	0.02 (0.06)	0.68	0.08 (0.06)	0.17	−0.003 (0.06)	0.96	−0.04 (0.06)	0.57
Conventional lipids								
Total cholesterol (mg/dl)	0.05 (0.05)	0.36	0.06 (0.05)	0.26	−0.02 (0.06)	0.70	−0.03 (0.06)	0.62
Triglyceride (mg/dl)	0.13 (0.05)	**0.005**	0.11 (0.05)	**0.02**	−0.001 (0.08)	0.99	0.03 (0.08)	0.68
LDL cholesterol (mg/dl)	0.003 (0.05)	0.95	0.01 (0.05)	0.84	−0.03 (0.06)	0.66	−0.02 (0.06)	0.76
Non-HDL cholesterol (mg/dl)	0.04 (0.05)	0.45	0.04 (0.05)	0.16	−0.02 (0.06)	0.70	−0.01 (0.06)	0.87
HDL cholesterol (mg/dl)	0.04 (0.06)	0.59	0.09 (0.06)	0.16	−0.002 (0.06)	0.97	−0.05 (0.06)	0.42

*Models were adjusted for DCCT randomization, albumin excretion rate, HbA_{1C}, diabetes duration, body mass index, and current smoking at DCCT baseline (1983–89). The regression models were also adjusted for statin use (any time during the DCCT baseline to EDIC year 12), ultrasound devices, and image readers at EDIC year 12.

P values in bold if significant (<0.05).

Table 5

DCCT baseline lipoprotein profiles vs. internal carotid IMT change from EDIC year 1 to year 12 (year12–year1) (Standardized linear regression coefficients)

Variables	Men (n=242)				Women (n=203)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
NMR subclasses	Slope(SE)	P	Slope(SE)	P	Slope(SE)	P	Slope(SE)	P
Total VLDL and chylomicrons (nmol/L)	0.01 (0.07)	0.92	−0.06 (0.07)	0.40	0.07 (0.06)	0.21	0.08 (0.06)	0.15
Large VLDL & chylomicrons (nmol/L)	0.06 (0.07)	0.37	0.02 (0.08)	0.77	0.01 (0.06)	0.93	0.03 (0.06)	0.64
Medium VLDL (nmol/L)	−0.04 (0.07)	0.53	−0.76 (0.07)	0.28	0.06 (0.07)	0.32	0.11 (0.07)	0.10
Small VLDL (nmol/L)	0.03 (0.07)	0.69	−0.04 (0.07)	0.60	0.06 (0.05)	0.26	0.06 (0.05)	0.31
Total IDL/LDL (nmol/L)	0.15 (0.07)	**0.04**	0.06 (0.08)	0.41	−0.004 (0.06)	0.94	0.02 (0.06)	0.70
IDL (nmol/L)	−0.04 (0.08)	0.63	−0.09 (0.08)	0.26	−0.01 (0.05)	0.82	0.02 (0.05)	0.77
Large LDL (nmol/L)	0.05 (0.08)	0.52	−0.01 (0.08)	0.95	−0.02 (0.06)	0.72	−0.03 (0.06)	0.59
Small LDL (nmol/L)	0.11 (0.07)	0.12	0.08 (0.07)	0.26	0.02 (0.06)	0.77	0.04 (0.06)	0.50
Total HDL (μmol/L)	−0.02 (0.08)	0.77	−0.04 (0.08)	0.61	−0.06 (0.05)	0.24	−0.09 (0.05)	0.07
Large HDL (μmol/L)	−0.17 (0.08)	**0.039**	−0.11 (0.08)	0.19	0.0001 (0.05)	1.00	−0.01 (0.06)	0.88
Medium HDL (μmol/L)	0.14 (0.09)	0.11	0.13 (0.09)	0.13	−0.05 (0.05)	0.33	−0.06 (0.05)	0.23
Small HDL (μmol/L)	−0.05 (0.08)	0.51	−0.10 (0.08)	0.21	−0.01 (0.05)	0.87	−0.03 (0.05)	0.59
NMR particle diameter								
VLDL particle size (nm)	0.05 (0.07)	0.52	0.06 (0.07)	0.41	−0.05 (0.06)	0.48	−0.0003 (0.07)	1.00
LDL particle size (nm)	−0.03 (0.07)	0.70	−0.04 (0.07)	0.60	−0.02 (0.06)	0.71	−0.03 (0.06)	0.61
HDL particle size (nm)	−0.14 (0.08)	0.06	−0.09 (0.08)	0.28	0.04 (0.06)	0.50	0.04 (0.06)	0.52
Conventional lipids								
Total cholesterol (mg/dl)	0.11 (0.07)	0.14	0.03 (0.08)	0.68	−0.07 (0.06)	0.24	−0.07 (0.06)	0.19
Triglyceride (mg/dl)	0.16 (0.06)	**0.01**	0.12 (0.07)	0.08	0.09 (0.07)	0.20	0.14 (0.08)	0.08
LDL cholesterol (mg/dl)	0.12 (0.07)	0.11	0.04 (0.08)	0.56	−0.09 (0.06)	0.12	−0.10 (0.06)	0.09
Non-HDL cholesterol (mg/dl)	0.14 (0.07)	**0.048**	0.06 (0.08)	0.47	−0.06 (0.06)	0.28	−0.07 (0.06)	0.26
HDL cholesterol (mg/dl)	−0.12 (0.09)	0.17	−0.07 (0.09)	0.42	−0.02 (0.05)	0.74	−0.03 (0.05)	0.53

*Models were adjusted for DCCT randomization, albumin excretion rate, HbA_{1C}, diabetes duration, body mass index, and current smoking at DCCT baseline (1983–89). The regression models were also adjusted for statin use (any time during the DCCT baseline to EDIC year 12), ultrasound devices, and image readers at EDIC year 12.

P values in bold if significant (<0.05).