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

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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.
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.

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

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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 1441 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: 27–34 nm), intermediate density lipoprotein (IDL) (23–37 nm), 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].