



Plasma triglycerides predict incident albuminuria and progression of coronary artery calcification in adults with type 1 diabetes: The Coronary Artery Calcification in Type 1 Diabetes Study

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BACKGROUND: Coronary artery disease and diabetic nephropathy, which are thought to share pathogenic mechanisms, remain the most common causes of mortality in type 1 diabetes (T1D). Data from basic and clinical studies indicate that hypertriglyceridemia plays an important role in the pathogenesis of vascular complications, but the role of triglycerides (TG) in the normal range remains unresolved in T1D.

OBJECTIVE: We hypothesized that fasting TG would independently predict cardiorenal disease in adults with T1D and normal-to-low levels of TG.

METHODS: Subjects (N = 652) were 19 to 56 years old at baseline and reexamined 6 years later. Urinary albumin excretion was measured, and categorized as microalbuminuria or greater. Progression of coronary artery calcification (CACp), measured using electron beam computed tomography, was defined as a change in the square root transformed CAC volume ≥ 2.5 . The association of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein B, non-HDL-C, natural log triglyceride (lnTG), ln(TG/HDL-C) ratio with CACp and incident albuminuria were examined in logistic regression. The models were adjusted for age, sex, T1D duration, hemoglobin A1c, systolic blood pressure, diastolic blood pressure, blood pressure medications, statins, and smoking status. Integrated discrimination index and net reclassification improvement were used to examine prediction performance.

RESULTS: Incident albuminuria was independently associated with CACp. lnTG independently predicted both incident albuminuria (odds ratio: 1.53, 1.02–2.30, $P = .04$) and CACp (1.41, 1.11–1.80, $P = .006$). The addition of lnTG to ABC risk factors (HbA1c, systolic blood pressure, diastolic blood

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pressure, and LDL-C) moderately improved discrimination and reclassification of CACp and incident albuminuria.

CONCLUSION: In adults with T1D, fasting TG independently predicted cardiorenal disease over 6 years and improved reclassification of risk by conventional risk factors.

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Background

Cardiorenal complications cause the majority of deaths in type 1 diabetes.^{1,2} Diabetic nephropathy (DN) accounts for almost half of end-stage renal disease in the United States,¹ and the risk of mortality from coronary artery disease (CAD) is exceptionally high in type 1 diabetes and almost 4-fold greater than what is observed in those without diabetes.² CAD and DN have been proposed to be manifestations of the same underlying pathology and also exist as interrelated risk factors.^{3,4} The increased mesangial matrix associated with DN is similar to the pathophysiology of atherosclerosis.³ The shared pathogenic mechanisms imply common risk factors and therapeutic targets, including hypertension, glycemic control, and dyslipidemia.⁵

Advances in the management of conventional risk factors over the past 2 decades, however, have improved the outcome of microvascular complications, whereas the prevalence of macrovascular complications is on the rise.⁶ Lipids remain part of the conventional risk factors for DN⁷ and atherosclerosis.^{8,9} Low-density lipoprotein cholesterol (LDL-C), the only lipid variable accounted for in the American Diabetes Association's (ADA) ABC goals (A: hemoglobin A1c [HbA1c] <7.0%, B: blood pressure [BP] < 130/80 mm Hg, C: LDL-C <100 mg/dL),¹⁰ did not predict progression of subclinical coronary atherosclerosis and incident albuminuria in adults with type 1 diabetes in the Coronary Artery Calcification in Type 1 Diabetes Study.¹¹ Data from adults with and without type 2 diabetes suggest that alternative lipid markers including triglycerides (TG) may be superior to LDL-C in predicting CAD and DN.^{12,13} There is good evidence that hypertriglyceridemia is an important risk factor of vascular complications in type 1 diabetes,^{8,13} but to what extent TG contribute to vascular complications outside the hypertriglyceridemia range is less clear. We hypothesized that TG would independently predict both incident albuminuria and coronary artery calcification (CACp) in adults with type 1 diabetes and low-to-normal levels of TG over a 6-year period. Second, we hypothesized that the association between TG and cardiorenal complications would be stronger than the associations with alternative lipid indices including LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, apolipoprotein B, and TG/HDL-C. Finally, we hypothesized that the addition of TG to systolic BP (SBP), diastolic BP (DBP), HbA1c, and LDL-C (ABC risk factors) would improve the risk discrimination and classification of cardiorenal disease.

Methods

The Coronary Artery Calcification Trial in type 1 Diabetes Study enrolled 1416 subjects 19 to 56 years old, 652 with type 1 diabetes and 764 without diabetes, who were asymptomatic for cardiovascular disease (CVD) at the baseline visit in 2000–2002 and then were reexamined 3 and 6 years later. Only the 652 participants with type 1 diabetes were included in this analysis. The flowchart of subject selection for this analysis is depicted in Figure 1. The study was approved by the Colorado Multiple Institutional Review Board and all participants provided informed consent.

We measured height and weight, and calculated body mass index (BMI) in kg/m². Resting systolic (SBP) and fifth-phase DBP were measured 3 times while the patient was seated, and the second and third measurements were averaged. After an overnight fast, blood was collected, centrifuged, and separated. Plasma was stored at 4°C until assayed. Total plasma cholesterol and TG levels were measured using standard enzymatic methods, HDL-C was separated using dextran sulfate and measured by enzymatic methodology (Beckman Coulter), and LDL-C was calculated using the Friedewald formula at University of Colorado Denver CTCRC Laboratory. Non-HDL-C was calculated by subtracting HDL-C from total cholesterol, and the ratio of TG to HDL-C was calculated by dividing TG by HDL-C. ApoB was measured by Beckman Array Nephelometer (Beckman Coulter Inc., Brea, CA). High-performance liquid chromatography was used to measure HbA1c (HPLC, Bio-Rad variant).

Incident albuminuria

Albuminuria was defined as albumin excretion rate (AER) ≥ 20 $\mu\text{g}/\text{min}$ if timed urine samples were obtained, or albumin/creatinine ratio (ACR) ≥ 30 mg/g for spot samples (if timed urine was not available). Overnight urine samples were collected and urine creatinine and albumin were measured (RIA, Diagnostic Products). At both visits, urinary AER and/or ACR were measured. Of the 27 subjects who developed incident albuminuria all had AER calculated, and all but 2 ($n = 326/328$) of those who did not develop incident albuminuria had AER calculated.

Progression of coronary artery calcification

Coronary artery calcification (CAC) measurements were obtained in duplicate using an ultrafast Imatron C-150XLP

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