Published in final edited form as:

Atherosclerosis. 2010 June ; 210(2): 671–673. doi:10.1016/j.atherosclerosis.2009.12.034.

Higher Fibrinogen Levels Predict Progression of Coronary Artery Calcification in Adults with Type 1 Diabetes

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Abstract

Aim—To determine whether fibrinogen levels predict independently progression of coronary artery calcification (CAC) in adults with type 1 diabetes.

Methods—Data from a prospective cohort - the Coronary Artery Calcification in Type 1 Diabetes Study - were evaluated. Fibrinogen levels at baseline were separated into quartiles. CAC was measured twice and averaged at baseline and at follow-up 2.4 ± 0.4 years later. CAC progressors were defined as participants whose square-root transformed CAC volume increased by $\geq 2.5^3$ or development mm of clinical coronary artery disease during the follow-up period.

Results—Fibrinogen levels were higher in progressors than in non-progressors (276 ± 61 mg/dl versus 259 ± 61 mg/dl, $p = 0.0003$). CAC progression, adjusted for known cardiovascular risk factors, increased in the highest quartile.

Conclusions—Higher fibrinogen levels predict CAC progression in type 1 diabetes subjects, independent of standard cardiovascular risk factors.

Keywords

type 1 diabetes; coronary artery calcification; fibrinogen

Introduction

Fibrinogen levels have been associated with coronary artery disease (CAD) in men with type 1 diabetes, beyond the effect of established risk factors (1). Hyperfibrinogenemia leads to enhanced coagulant activity and is associated with increased blood viscosity (2); fibrinogen is also a cofactor in plaque activation and may directly contribute to plaque formation, where it is converted to fibrin and fibrinogen degradation products (3). Additionally, hyperfibrinogenemia may be an indicator of inflammatory vascular changes and endothelial dysfunction (4). Higher fibrinogen levels also predictor development of atherosclerosis in young adults without diabetes (5). In this paper, we evaluated fibrinogen levels as a possible

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Disclosure: There is no conflict of interest to disclosure.

independent predictor of progression of coronary artery calcification (CAC) using data from a prospective cohort - the Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study (6).

Research Design and Methods

Of the 1,416 individuals enrolled at baseline, 1186 had data on CAC progression and complete information about covariates evaluated. Thus, the study population included 546 participants with type 1 diabetes and 640 non-diabetic controls; all were asymptomatic for CAD and had no history of coronary artery bypass graft surgery, myocardial infarction, coronary angioplasty, or angina at baseline. The entire cohort performed clinical and laboratory evaluation according to a standard protocol and completed a standardized questionnaire as reported previously (6, 7). All participants underwent a coronary calcium scan using an ultrafast Imatron C-150XLP EBCT scanner (GE/Imatron, San Francisco, CA) to obtain two sets of high resolution, noncontrast, contiguous 3-mm tomographic images acquired at 100-ms exposure. CAC was measured twice at the baseline and twice at a follow-up 2.4 ± 0.4 years later and averaged at each visit. Methodology for CAC has been described previously (7-9). CAC Progressors were defined as participants whose square-root transformed CAC volume increased by $\geq 2.5 \text{ mm}^3$ or development of clinical coronary artery disease during the follow-up (10). Fibrinogen was measured in an automated clot-rate assay using the Sta-r instrument in the laboratory of Dr. Russell Tracy at the University of Vermont, and it was expressed in mg/dl.

The study protocol was reviewed and approved by the Colorado Combined Institutional Review Board, and informed consent was obtained from all participants.

Statistical Analysis

Data are presented as arithmetic means and SDs for continuous variables (geometric means and ranges for log-transformed variables) and percentages for categorical variables. Two-sample *t* test was used for continuous variables and the χ^2 test was used for categorical variables. To evaluate the relationship between fibrinogen levels and progression of CAC, we first divided fibrinogen levels in quartiles and next fit a base model 1 for logistic regression including age (per 10 years), gender, CAC volume at baseline and quartiles of fibrinogen as predictor variables and CAC progression as the outcome. We then fit a model adjusted for cardiovascular risk factors (systolic and diastolic blood pressure (BP), LDL and HDL cholesterol and smoking status). Next, we sought parsimonious models that included only those variables that were independently associated with the outcome in a stepwise selection procedure ($p < 0.15$ as the criteria for entry and $p < 0.10$ for removal). Next, a model was fit that considered additional risk factors such as body mass index (BMI), HbA1c, log triglycerides and log albumin excretion rate (AER).

SAS 9.2 (SAS Institute, Cary, North Carolina) was used to perform these analyses, with $p < 0.05$ considered significant.

Results

Table 1 shows the clinical and laboratory characteristics at baseline stratified by CAC progression. Progressors ($n = 206$, 17.3%) were more frequently male, older, with type 1 diabetes ($n = 139$, 67%), had higher BMI, higher systolic and diastolic BP, higher CAC volume score at baseline, lower HDL cholesterol, higher triglycerides levels, higher HbA1c, higher AER and were more frequently taking statins than non-progressors. Fibrinogen levels were higher in progressors than in non-progressors; however, fibrinogen levels were not different between type 1 diabetes and non-DM subjects ($267 \pm 67 \text{ mg/dl}$ vs. $261 \pm 60 \text{ mg/dl}$, $p = 0.06$). When fibrinogen was stratified in quartiles (1st quartile $\leq 224.2 \text{ mg/dl}$, 2nd quartile is between

224.3 and 256 mg/dl, 3rd quartile is between 256.1 and 299.5 mg/dl and 4th quartile is > 299.5 mg/dl), there were more progressors in the highest quartile in comparison to lower quartiles in type 1 diabetes subjects ($p = 0.005$), but not in non-diabetic controls ($p = 0.27$). To evaluate the association between higher fibrinogen levels and CAC progression, multiple logistic regression models including only type 1 diabetes subjects, were performed as described above. Fibrinogen levels in the 4th quartile increased the risk for CAC progression 2.92 times [(95% CI: 1.36 – 6.27), $p = 0.005$], 2.53 times [(95% CI: 1.20 – 5.31), $p = 0.01$] and 2.62 times [(95% CI: 1.25 – 5.49), $p = 0.01$], in comparison to 1st, 2nd and 3rd quartiles respectively. Figure 1 shows the association of fibrinogen levels with CAC progression after adjustments. There was no interaction between the effect of fibrinogen and gender.

Discussion

The main finding this study is that elevated levels of fibrinogen predict CAC progression in type 1 diabetes subjects. Recently, higher fibrinogen levels have been associated with subsequent atherosclerosis assessed by CAC and carotid thickness in young adults (5); however, Green et al did not measure CAC at baseline, they only suggested that calcification would likely not have been detected if the exam had been done, because their population was young. We found an association between fibrinogen levels and CAC progression in our cohort of T1D subjects. In non-DM controls we did not observe this association, however CAC progression was more frequent in T1D subjects than in controls (67% from progressors were T1D versus while only 33% were non-DM controls, $p < 0.0001$); this could justify the lack of effect of fibrinogen in CAC progression in controls.

The presences of fibrinogen, fibrin, and LDL cholesterol have been detected in atherosclerotic plaques, suggesting that a common mechanism may exist for fibrinogen and lipoprotein entry into the vessel wall (11,12). The potential involvement of fibrinogen in the pathogenesis of atherosclerosis is supported by the demonstration that fibrinogen induces endothelial cell disorganization and migration, stimulates smooth muscle proliferation, and enhances the release of endothelial cell-derived growth factors (13).

Previously, Soedamah-Muthu et al (1) demonstrated that fibrinogen levels predicted coronary heart disease; however this effect was reported only in men with type 1 diabetes. The results of previous studies have shown inconsistent gender effect (1,5,14), our results suggest similar association between fibrinogen and vascular complications in men and women. Fibrinogen levels may be associated with nephropathy in type 1 diabetes subjects (2); importantly our analyses were adjusted for AER.

Highest fibrinogen levels in comparison to lowest levels have recently been associated with presence of subclinical atherosclerosis in a large population-based study, independent of the adjustment for known cardiovascular risk factors. However this association was only modest and then disappeared when the association with CAC burden was considered (15). Previous studies have shown a weak association between the presence of CAC and fibrinogen levels (14). These results, in addition to our finding, support the idea that inflammatory biomarkers and CAC could offer integrative information about CAD. Additionally we reported, for the first time, that higher fibrinogen levels predict CAC progression in type 1 diabetes subjects, independently of standard cardiovascular risk factors.

Acknowledgments

This study was supported by the National Institutes of Health National Heart, Lung and Blood Institute grants R01 HL61753 and R01 HL079611, and Diabetes Endocrinology Research Center Clinical Investigation Core P30 DK57516. The study was performed at the Adult General Clinical Research Center at the University of Colorado Denver Anschutz Medical Center supported by the NIH M01 RR000051, at the Barbara Davis Center for Childhood

Diabetes in Denver, CO, and at Colorado Heart Imaging Center in Denver, CO. TCR was supported by a scholarship from CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).

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Figure 1.

Incidence of CAC progression by fibrinogen quartiles at baseline in type 1 diabetes and non – DM subjects.

* p = 0.005 compared to 4th quartile and adjusted for age (per 10 years), gender, CAC volume at baseline, systolic blood pressure, HbA1c, body mass index, triglycerides and albumin excretion rate.

§ p = 0.01 compared to 4th quartile and adjusted for the adjusted for age per 10 years, sex, CAC volume at baseline, systolic and diastolic blood pressure, HDL cholesterol, HbA1c, body mass index, triglycerides and albumin excretion rate.

1st quartile ≤ 224.2 mg/dl, 2nd quartile is between 224.3 and 256 mg/dl, 3rd quartile is between 256.1 and 299.5 mg/dl and 4th quartile is > 299.5 mg/dl.

Table 1

Clinical and laboratory characteristics at baseline between progressors and non-progressors.

	Progressors N = 206	Non-progressors N = 980	P
Age (years)	44 ± 8	37 ± 9	<.0001
Male (%)	65	41	<.0001
Type 1 diabetes (%)	67	40	0.03
Smoking current (%)	12	7	0.03
Smoking ever (%)	22	19	0.31
BMI (kg/m ²)	27 ± 4	25 ± 4	<.0001
Systolic BP (mm Hg)	123 ± 13	114 ± 12	<.0001
Diastolic BP (mm Hg)	80 ± 9	77 ± 8	<.0001
CVS at baseline (mm ³)	7.16 ± 9.44	0.76 ± 2.39	<.0001
Total cholesterol (mg/dl)	185 ± 39	184 ± 37	0.60
HDL cholesterol (mg/dl)	51 ± 16	54 ± 15	0.04
LDL cholesterol (mg/dl)	110 ± 32	108 ± 32	0.40
Triglycerides (mg/dl)	102 (32-758)	93 (25-1060)	0.03
HbA1c (%)	7.3 ± 1.5	6.4 ± 1.5	<.0001
AER (mg/L)	11 (1,0-4059)	1,1 (0,5-1919)	<.0001
Statin use (%)	25	8	<.0001
Fibrinogen (mg/dl)	276 ± 61	259 ± 61	0.0003

Data are means ± SD, % or geometric means (range). BMI: body mass index; BP: blood pressure; CVS: calcium volume score; AER: albumin excretion rate.