Family history of diabetes and the risk of subclinical atherosclerosis


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Abstract

Aim. – This study investigated the influence of a family history of diabetes on the risk of subclinical coronary atherosclerosis according to coronary computed tomography angiography (CCTA) in asymptomatic individuals.

Methods. – A total of 6434 consecutive asymptomatic individuals with no prior history of coronary artery disease voluntarily underwent CCTA evaluation as part of a general health examination. Coronary atherosclerotic plaque and significant coronary artery stenosis (degree of stenosis ≥50%) on CCTA were assessed. Logistic regression analysis was used to determine the association between a family history of diabetes and atherosclerotic plaque or significant coronary artery stenosis according to the degree of diabetes (normal, prediabetic and diabetic).

Results. – Mean age of study participants was 53.7 ± 7.6 years, and 4694 (73.0%) were male. A total of 1593 (24.8%) participants had a family history of diabetes in a first-degree relative. Among the study participants, 1115 (17.3%), 3122 (48.5%) and 2197 (34.1%) were categorized as diabetic, prediabetic and normal, respectively. In diabetic participants, after stepwise adjustments for clinical and laboratory variables, a family history of diabetes was significantly associated with non-calcified plaque (P < 0.05 for all), but did not appear to be associated with either calcified or mixed plaques or with significant coronary artery stenosis (P > 0.05 for all). In prediabetic and normal participants, a family history of diabetes was not associated with either atherosclerotic plaque or significant coronary artery stenosis (P > 0.05 for all).

Conclusion. – In asymptomatic diabetic individuals, a family history of diabetes is consistently associated with non-calcified coronary plaque after adjusting for risk factors.

Keywords: Atherosclerosis; Coronary artery disease; Diabetes; Family history

1. Introduction

Coronary artery disease (CAD) is a major cause of death and disability all across the globe [1]. Although CAD mortality rates have declined with advances in medical fields over the past decades, CAD still remains the leading cause of death in adults [2]. Moreover, the first clinical manifestation is often asymptomatic until the onset of sudden cardiac death or myocardial infarction [3]. Therefore, there has been substantial interest in the early detection and treatment of subclinical stages of CAD [4].

A family history of diabetes is known to be associated with an increased risk of developing diabetes mellitus [5]. Individuals with a family history of diabetes have a more atherogenic
pattern of cardiovascular risk factors than those without [6,7]. These findings suggest that a genetic predisposition to diabetes could contribute to subclinical development of CAD in susceptible individuals. However, previous studies of intima-media thickness, a known surrogate marker of coronary atherosclerosis, have reported inconsistent results [8–10], and it is still uncertain whether a family history of diabetes has any impact on risk for subclinical CAD.

Recently, with the advent of multidetector-row computed tomography, coronary computed tomography angiography (CCTA) has become widely used in the comprehensive evaluation of coronary atherosclerosis, including lesion location, severity and plaque characteristics [11]. However, there are limited data on the impact of a family history of diabetes on subclinical atherosclerosis, as assessed by CCTA. Therefore, through a large cohort who voluntarily underwent CCTA screening tests for early detection of CAD, the present study aimed to assess the influence of a family history of diabetes on the risk of subclinical coronary atherosclerosis.

2. Methods

2.1. Study population

From January 2007 to December 2011, 9269 consecutive South Korean individuals, aged ≥20 years, who had undergone self-referred CCTA evaluation as part of a general health examination at the Health Screening and Promotion Center in the Asan Medical Center (AMC) were enrolled into the study. All were made aware of the possible risks associated with CCTA. A total of 7129 (76.9%) individuals consented to participate. Excluded were subjects with:

- a previous history of angina or myocardial infarction;
- abnormal resting electrocardiography (ECG) results, such as pathological Q waves, ischaemic ST segments, T-wave changes or left bundle-branch blocks;
- insufficient medical records;
- structural heart disease;
- a previous history of open-heart surgery or percutaneous coronary intervention;
- a previous cardiac procedure;
- renal insufficiency (creatinine >1.5 mg/dL).

Ultimately, 6434 subjects were enrolled (Fig. 1).

The study was approved by the local Institutional Review Board of the AMC in Seoul, Korea. All participants gave their written informed consent.

Basic demographic data for the recruited subjects were acquired from a database maintained by the Health Screening and Promotion Center at the AMC. A family history of diabetes or CAD, and a medical history of angina, myocardial infarction, stroke, structural heart disease, open-heart surgery, percutaneous coronary intervention, previous cardiac procedures, diabetes mellitus, hypertension, hyperlipidaemia and smoking status were collected from responses to a systematic self-reported questionnaire issued prior to the general health examination.

A family history of diabetes or of CAD was defined as having a first-degree relative of any age, according to the self-reported questionnaire [12]. Diabetes was defined as either fasting plasma glucose (FPG) ≥126 mg/dL or haemoglobin A1c (HbA1c) levels ≥6.5% [13]. In addition, subjects who self-reported the use of antidiabetic medications were considered to have diabetes [14]. Prediabetes was defined as an FPG of 100–125 mg/dL, or HbA1c levels of 5.7–6.4% [13]. Hypertension was defined as blood pressure (BP) ≥140/90 mmHg or a self-reported history of hypertension and/or use of antihypertensive medication. Hyperlipidaemia was defined as a total cholesterol ≥240 mg/dL or use of antihyperlipidaemic treatment.

2.2. Clinical and laboratory measurements

Height and weight were obtained with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilogrammes divided by the square of height in meters (kg/m²). Waist circumference (cm) was measured midway between the lower costal margin and ilioc crest at the end of a normal expiration of breath. BP was measured on the right arm after a rest of ≥5 min, using an automatic manometer and an appropriate cuff size [15].

After overnight fasting, early-morning blood samples were drawn from the antecubital vein into vacuum tubes and subsequently analyzed by a certified central laboratory at the AMC. Measurements included concentrations of FPG, insulin, creatinine and several lipid parameters. Fasting total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and creatinine were measured by an enzymatic colorimetric method, using a TBA 200FR NEO analyzer (Toshiba Medical Systems Co. Ltd., Tokyo, Japan). FPG was measured by an enzymatic colorimetric method using a TBA 200FR auto-analyzer (Toshiba). Serum insulin was measured by immunoradiometric assay (TFB Inc., Tokyo, Japan). Ion-exchange high-performance liquid chromatography (Bio-Rad Laboratories, Inc., Hercules, CA, USA) was used to measure HbA1c levels. Homoeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated as the product of fasting serum insulin (μU/mL) and FPG (mg/dL) concentrations divided by 405. All enzyme activity was measured at 37 °C [15].

2.3. Image acquisition and analysis

CCTA was conducted using either single-source 64-slice CT (Lightspeed VCT, GE Healthcare, Milwaukee, WI, USA) or dual-source CT (Somatom Definition, Siemens Healthcare, Erlangen, Germany). Subjects with no contraindication to β-adrenergic blocking agents and an initial heart rate >65 beats/min received an oral dose of 2.5 mg bisoprolol (Concor®, Merck KGaA, Darmstadt, Germany) 1 h before CT examination. CT scanning was performed with either the prospective ECG-triggering mode or retrospective ECG-gating mode, using ECG-based tube current modulation. Two puffs (2.5 mg) of isosorbide dinitrate (Isokel® spray, Schwarz Pharma, Monheim, Germany) were delivered into the patient’s mouth before contrast injection. During CCTA acquisition, a 60–80 mL dose of
iodinated contrast medium (Iomeron 400, Bracco Imaging SpA, Milan, Italy) was injected at 4 mL/s, followed by a 40-mL saline flush. The region of interest was placed on the ascending aorta, and image acquisition was automatically initiated once the selected threshold (100 HU) was reached, using bolus tracking. A standard scanning protocol was used, with the tube voltage and tube current–time product adjusted according to the patient’s body size as follows: 100 or 120 kVp tube voltage; 240–400 mAs per rotation (dual-source CT); and 400–800 mA (64-slice CT) tube current. A size-specific dose estimate was calculated using the patient’s body diameter. The mean effective dose of the CT protocol was 7.6 ± 5.1 mSv [11].

All CCTA scans were analyzed at a dedicated workstation (Advantage Workstation, GE, or Volume Wizard, Siemens) by experienced cardiovascular radiologists (D.H.Y., J.-W.K., and T.-H.L.). As per the guidelines of the Society of Cardiovascular Computed Tomography, a 16-segment coronary artery tree model was used [16]. A Coronary Artery Calcium Score (CACS) was measured as described elsewhere [17], and categorized into scores of 0, 1–10, 11–100, 101–400 and >400 [18]. Plaques were defined as structures >1 mm² within and/or adjacent to the vessel lumen that could be clearly distinguished from the lumen and surrounding pericardial tissue. Plaques containing calcified tissue involving >50% of the plaque area (density >130 HU) were classified as calcified, while plaques that were <50% calcium were classified as mixed, and plaques with no calcium were classified as non-calcified lesions [19]. The contrast-enhanced portion of the coronary lumen was semi-automatically traced at the site of maximum stenosis, and compared with the mean value of the proximal and distal reference sites [20]. Stenosis ≥50% was defined as significant.

### 2.4. Statistical analysis

Categorical data were compared using Chi² statistics and Fisher’s exact test. Continuous variables were analyzed using unpaired Student’s t test, non-parametric Mann-Whitney test and one-way analysis of variance or non-parametric Kruskal-Wallis test. The relationships between a family history of diabetes and coronary atherosclerotic plaques or significant coronary artery stenosis on CCTA were assessed by logistic regression analysis, with adjustment for clinical variables such as age, gender, BMI, waist circumference, mean BP, current smoking and family history of CAD. Further adjustments for laboratory variables such as FPG, HbA₁c, fasting insulin, HOMA-IR, and LDL cholesterol were also made. All reported P-values were two-sided, and P < 0.05 was considered statistically significant. Data manipulation and statistical analyses were conducted using SAS® version 9.1 software (SAS Institute Inc., Cary, NC, USA).

### 3. Results

#### 3.1. Baseline characteristics

The mean age of the study population was 53.7 ± 7.6 years, and 4694 (73.0%) participants were male. Baseline characteristics of the study population according to a family history of diabetes are presented in Table 1. Individuals with a family history of diabetes were younger and had a higher BMI, a more pronounced family history of CAD, higher rates of hyperlipidaemia and diabetes, and higher levels of FPG, insulin, HbA₁c and HOMA-IR compared with those without. Among

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**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetic Family History</th>
<th>No Diabetic Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.7 ± 7.4</td>
<td>54.0 ± 7.6</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>73.0%</td>
<td>69.0%</td>
</tr>
<tr>
<td>BMI</td>
<td>28.2 ± 3.4</td>
<td>27.7 ± 3.3</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>89.3 ± 12.9</td>
<td>88.7 ± 12.3</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>123.5 ± 16.2</td>
<td>121.9 ± 15.8</td>
</tr>
<tr>
<td>Current smoking</td>
<td>29.4%</td>
<td>25.5%</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>48.1%</td>
<td>36.2%</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>109.6 ± 24.6</td>
<td>108.5 ± 24.3</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>49.1 ± 14.0</td>
<td>48.7 ± 13.8</td>
</tr>
<tr>
<td>Fasting insulin (mU/mL)</td>
<td>8.6 ± 5.7</td>
<td>7.9 ± 4.9</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.4 ± 0.7</td>
<td>1.2 ± 0.6</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>6.4 ± 0.9</td>
<td>6.0 ± 0.7</td>
</tr>
</tbody>
</table>

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the study participants, 1115 (17.3%), 3122 (48.5%) and 2197 (34.1%) were categorized as diabetic, prediabetic and normal, respectively. Those with diabetes were older and had more comorbid conditions than the prediabetic and normal subjects (Table S1; see supplementary material associated with this article online).

### 3.2. CCTA findings

Table 2 shows the CCTA findings. The mean CACS of the participants was 40.8 ± 139.5. There was no significant difference in CACS between those with and without a family history of diabetes (39.4 ± 125.3 vs. 41.2 ± 143.9; P = 0.652). Atherosclerotic plaques were detected in 2691 (41.8%) participants, with calcified, non-calcified and mixed plaques found in 1810 (28.1%), 1180 (18.3%) and 580 (8.9%) subjects, respectively. However, the prevalences of any, calcified, non-calcified and mixed plaques did not statistically differ between individuals with and without a family history of diabetes. Of the study participants, CCTA revealed that 494 (7.7%) had significant coronary artery stenosis (≥50%). The prevalence of significant coronary artery stenosis did not differ between those with and without a family history of diabetes (132 [8.3%] vs. 362 [7.5%]; P = 0.293).

Table S2 (see supplementary material associated with this article online) presents the CCTA findings according to degree of diabetes. Diabetic individuals had higher CACS than prediabetic and normal individuals (77.9 ± 194.6 vs. 38.5 ± 135.4 and 25.1 ± 103.9, respectively; P < 0.001). The incidences of atherosclerotic calcified, non-calcified and mixed plaques were all significantly higher in diabetic individuals (P < 0.001). Those with diabetes also had more significant coronary artery stenosis than the prediabetic and normal individuals (158 [14.2%] vs. 224 [7.2%] and 112 [5.1%], respectively; P < 0.001).

### 3.3. Association between family history of diabetes and subclinical atherosclerosis

In diabetic participants after stepwise adjustments for clinical variables (age, gender, BMI and waist circumference), logistic regression analysis revealed a significant association between a family history of diabetes and non-calcified plaque (P < 0.05 for all). After further adjustments for clinical and laboratory...
variables (mean BP, current smoking, family history of CAD, FPG, HbA1c, fasting insulin, HOMA-IR, creatinine and LDL cholesterol), a family history of diabetes was consistently associated with non-calcified plaque (P < 0.05 for all).

However, a family history of diabetes did not appear to be associated with either calcified or mixed plaques or with significant coronary artery stenosis (P > 0.05 for all; Table 3). Also, in prediabetic and normal participants after controlling for clinical variables, a family history of diabetes was not associated with either atherosclerotic plaque or significant coronary artery stenosis (P > 0.05 for all). Moreover, further adjusting for laboratory variables showed no significant relationship between a family history of diabetes and subclinical coronary atherosclerosis (P > 0.05 for all; Table S3; see supplementary material associated with this article online).

4. Conclusion

The main finding of the present study was that, in asymptomatic diabetic individuals after adjusting for risk factors, a family history of diabetes is an independent predictor of non-calcified plaque. However, such a family history showed no association with either calcified or mixed plaques, or with significant coronary artery stenosis. Also, in asymptomatic prediabetic and normal individuals, a family history of diabetes is not associated with either atherosclerotic plaque or significant coronary artery stenosis.

People with a family history of diabetes have an increased risk of developing diabetes, with early defects in beta-cell secretion [5,21,22]. A recent study showed that changes in insulin secretion, the cornerstone of a genetic predisposition to diabetes, were associated with the incidence of hypertension [23]. In addition, those with a family history of diabetes are more likely to have metabolic abnormalities such as insulin resistance, obesity, hypertriglyceridaemia, low HDL cholesterol, high BP and hyperglycaemia [6,24]. These findings suggest that individuals who have a genetic predisposition to diabetes might be at higher risk of CAD than those with no such predisposition. Also, as CCTA has been proven to provide comprehensive information regarding coronary atherosclerosis [11], our study aimed to assess the impact of a family history of diabetes on the risk of subclinical atherosclerosis, as detected by CCTA.

In this study of asymptomatic diabetic individuals, a family history of diabetes was associated with non-calcified plaque on CCTA analysis. However, other atherosclerotic plaques and significant coronary artery stenosis did not differ between asymptomatic diabetic subjects with and without a family history of diabetes. Previous studies had revealed an association between the presence of non-calcified plaque and high-risk patients such as those with diabetes, hyperlipidaemia or a family history of CAD and smokers [25]. In addition, non-calcified plaque was significantly associated with higher levels of high-sensitivity C-reactive protein, an inflammatory biomarker of plaque instability [25,26]. Such findings indicate that non-calcified plaque is more vulnerable to plaque rupture and associated with poorer cardiovascular outcomes [25]. Furthermore, the risk of non-calcified plaque has been reported in several studies [27–29]. Motoyama et al. [27] revealed that non-calcified plaques and increased positive vessel remodeling, as detected by CCTA, occurred more frequently in patients with acute coronary syndrome. Even in asymptomatic individuals, non-calcified plaques were associated with potential cardiac risk [28]. However, previous studies of high-intensity statin therapy showed significant regression of coronary atherosclerosis with cardiovascular benefits in diabetic patients [30,31]. Thus, more aggressive medical treatments, including high-intensity statin administration, could be considered part of the management of asymptomatic diabetic patients with a family history of diabetes.

In the present study, for prediabetic and normal individuals, there was no association between a family history of diabetes and subclinical atherosclerosis on CCTA, irrespective of adjustments for clinical and biological variables. For this population, previous smaller studies found that those with a family history of diabetes had greater intima-media thicknesses than controls.
Table 3
Association of family history of diabetes with subclinical atherosclerosis in asymptomatic diabetic individuals.

<table>
<thead>
<tr>
<th>Diabetic population (n=1115)</th>
<th>Significant stenosis</th>
<th>Any plaque</th>
<th>Calcified plaque</th>
<th>Non-calcified plaque</th>
<th>Mixed plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.94 (0.67–1.32)</td>
<td>0.711</td>
<td>1.11 (0.88–1.41)</td>
<td>0.386</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.04 (0.74–1.47)</td>
<td>0.820</td>
<td>1.28 (1.00–1.66)</td>
<td>0.054</td>
<td>1.05 (0.81–1.35)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.05 (0.74–1.48)</td>
<td>0.791</td>
<td>1.30 (1.01–1.68)</td>
<td>0.043</td>
<td>1.06 (0.82–1.38)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.04 (0.74–1.47)</td>
<td>0.825</td>
<td>1.30 (1.01–1.67)</td>
<td>0.046</td>
<td>1.06 (0.82–1.37)</td>
</tr>
<tr>
<td>Model 4</td>
<td>0.95 (0.66–1.35)</td>
<td>0.753</td>
<td>1.23 (0.95–1.59)</td>
<td>0.117</td>
<td>1.04 (0.80–1.35)</td>
</tr>
<tr>
<td>Model 5</td>
<td>1.03 (0.73–1.46)</td>
<td>0.871</td>
<td>1.30 (1.00–1.68)</td>
<td>0.047</td>
<td>1.05 (0.81–1.36)</td>
</tr>
<tr>
<td>Model 6</td>
<td>0.96 (0.67–1.36)</td>
<td>0.806</td>
<td>1.26 (0.98–1.64)</td>
<td>0.075</td>
<td>1.04 (0.81–1.35)</td>
</tr>
<tr>
<td>Model 7</td>
<td>1.06 (0.74–1.50)</td>
<td>0.764</td>
<td>1.31 (1.01–1.69)</td>
<td>0.045</td>
<td>1.05 (0.81–1.36)</td>
</tr>
<tr>
<td>Model 8</td>
<td>0.99 (0.69–1.41)</td>
<td>0.932</td>
<td>1.28 (0.98–1.66)</td>
<td>0.066</td>
<td>1.04 (0.80–1.35)</td>
</tr>
<tr>
<td>Model 9</td>
<td>1.04 (0.73–1.48)</td>
<td>0.838</td>
<td>1.30 (1.00–1.68)</td>
<td>0.051</td>
<td>1.05 (0.81–1.36)</td>
</tr>
<tr>
<td>Model 10</td>
<td>1.03 (0.72–1.46)</td>
<td>0.897</td>
<td>1.29 (1.00–1.68)</td>
<td>0.055</td>
<td>1.04 (0.80–1.35)</td>
</tr>
<tr>
<td>Model 11</td>
<td>0.95 (0.66–1.36)</td>
<td>0.764</td>
<td>1.26 (0.97–1.64)</td>
<td>0.082</td>
<td>1.03 (0.79–1.34)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, gender; model 2: adjusted for age, gender, body mass index; model 3: adjusted for age, gender, waist circumference; model 4: adjusted for age, gender, waist circumference, HbA1c; model 5: adjusted for age, gender, waist circumference, HOMA-IR; model 6: adjusted for age, gender, waist circumference, fasting plasma glucose, insulin; model 7: adjusted for age, gender, waist circumference, mean blood pressure, current smoking, HOMA-IR; model 8: adjusted for age, gender, waist circumference, mean blood pressure, current smoking, fasting plasma glucose, insulin; model 9: adjusted for age, gender, waist circumference, mean blood pressure, current smoking, family history of CAD, creatinine, LDL cholesterol, HOMA-IR; model 10: adjusted for age, gender, waist circumference, mean blood pressure, current smoking, family history of CAD, creatinine, LDL cholesterol, fasting plasma glucose, insulin; OR: odds ratio; CI: confidence interval; HOMA-IR: Homoeostasis Model Assessment of Insulin Resistance; CAD: coronary artery disease; LDL: low-density lipoprotein.
with no family history of diabetes [8,9]. However, other studies found that non-diabetic subjects with a family history of diabetes were insulin-resistant, yet showed no increases in carotid intima-media thickness [10]. Our present results are in agreement with these findings and suggest that the combination of a family history of diabetes with chronic hyperglycaemia may be important in promoting the development of substantial coronary artery lesions.

Our study has several limitations. First, it was performed at a single center. Also, as all participants had voluntarily gone to the hospital for a general health examination, there is a potential for selection bias. A second potential limitation is the recall bias and possible errors concerning a family history of diabetes, both of which are inherent with patient self-reporting [32]. However, a previous validation study indicated that a self-reported family history is unlikely to exert any substantial bias on any estimated risks associated with a family history [32,33]. Third, our study population was exclusively Korean, which means that the applicability of our findings to other ethnic groups may be limited. Fourth, the number and type of diabetes cases in the family history might have different effects on subclinical atherosclerosis. However, as this was not specified in the family histories of diabetes collected in this study, additional studies are clearly needed to elucidate the impact of specific family histories of diabetes on subclinical atherosclerosis. Finally, CCTA has potential downsides, including radiation hazards, use of contrast and higher cost [11]. In this light, our study enrolled only volunteers, as the use of CCTA in asymptomatic individuals has yet to prove justifiable.

In summary, in this large observational study of asymptomatic individuals undergoing CCTA, a family history of diabetes was associated with non-calcified plaque in those with diabetes, supporting an increased cardiovascular risk. However, in prediabetic and normal individuals, having a family history of diabetes was not associated with subclinical coronary atherosclerosis. These findings now need to be confirmed in additional studies.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data (Tables S1–S3) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2015.09.004.

References


