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Original article

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

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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 A_{1c} (HbA_{1c}) 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 HbA_{1c} 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/m^2). Waist circumference (cm) was measured midway between the lower costal margin and iliac 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 HbA_{1c} 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 (Isoket® spray, Schwarz Pharma, Monheim, Germany) were delivered into the patient's mouth before contrast injection. During CCTA acquisition, a 60–80 mL dose of