

ORIGINAL ARTICLE

Relationship of Glycated Hemoglobin A1c, Coronary Artery Calcification and Insulin Resistance in Males Without Diabetes

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Background and Aims. We undertook this study to compare the prevalence of coronary artery calcification (CAC) across glycated hemoglobin A1c (HbA1c) in nondiabetic males and to evaluate the impact of insulin resistance on CAC in relation to HbA1c levels.

Methods. A cross-sectional study was performed in 18,504 adult males without diabetes mellitus and cardiovascular disease (CVD). CAC scores were measured by multidetector computed tomography; CAC was defined as a CAC score >0. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR). Subjects were grouped by HbA1c quartile ($\leq 5.4\%$, 5.4–5.6%, 5.7%, 5.8–6.4%).

Results. Thirteen percent of subjects ($n = 2,406$) had a CAC score >0. The prevalence of CAC increased with increasing HbA1c quartile (9.4%, 11.1%, 14.1%, 17.3%). Crude odds ratios (ORs) for CAC were 1.2, 1.58 and 2.01 for the HbA1c quartiles 2, 3, and 4 when compared with the first quartile. Mean HOMA-IR levels were different among HbA1c categories and CAC status. HOMA-IR levels were higher in subjects with CAC than in those without, except in the third HbA1c quartile. Stratification by HbA1c showed a significant association between CAC and insulin resistance only in the first (OR 1.67) and fourth (OR 1.33) HbA1c quartile. After adjustment for CV risk factors, insulin resistance remained an independent predictor of CAC only in the first HbA1c quartile.

Conclusions. Our study demonstrated that not only glucose status represented by HbA1c but also insulin resistance might be associated with CAC in non-diabetic Korean men. The magnitude of association of CAC with insulin resistance was greater in the lowest HbA1c quartile group. © 2015 IMSS. Published by Elsevier Inc.

Key Words: Coronary artery calcification, Glycosylated hemoglobin, Insulin resistance.

Introduction

Previously published studies have reported associations between glucose metabolism and coronary artery calcification (CAC). It has been reported that an increased risk of coronary atherosclerosis persists even in people with normal fasting plasma glucose (FPG) and impaired fasting glucose (IFG), not only type 2 diabetes mellitus (1,2). However, there are few studies examining the association between

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HbA1c and CAC in nondiabetic subjects, with conflicting results (3–5). Chang et al. reported that a higher HbA1c level was found to have a modest and independent association with CAC in a euglycemic population with FPG <100 mg/dL (3). However, results from the Multi-Ethnic Study of Atherosclerosis (MESA) study showed significant association between higher HbA1c and CAC in nondiabetic women, but not in non-diabetic men (4). Also, in Framingham Heart Study cohort, CAC was not associated with IFG after adjusting for potential confounders (5).

Recent meta-analyses have shown that insulin resistance in nondiabetic subjects is associated with increased cardiovascular disease (CVD) risk (6). In addition, previous cohort studies have found elevated CAC scores even in nondiabetic subjects who have evidence of insulin resistance (7,8). However, a study by Tanaka et al. reported CAC to be independently associated with both hyperinsulinemia and low insulin levels (9). Another study found that HOMA-IR did not predict CAC or its progression after adjusting for metabolic syndrome components (10).

To the best of our knowledge, no reports have been published regarding the effect of insulin resistance on CAC in nondiabetic subjects grouped by HbA1c level. The purpose of this study was to compare the prevalence of CAC by HbA1c level in nondiabetic males. Also, the aim of this study was to analyze the mean HOMA-IR levels according to the presence or absence of CAC across different HbA1c quartiles and to examine whether the associations between HbA1c and CAC varies by insulin resistance.

Materials and Methods

Subjects

This was a retrospective study comprised of 19,722 Korean males >20 years of age with no history of CVD in the Kangbuk Samsung Health Study (KSHS) who underwent comprehensive health examinations between 2010 and 2011 at Kangbuk Samsung Hospital Total Healthcare Center. Among these subjects, we excluded individuals with any of the following: FPG concentration ≥ 126 mg/dL ($n = 715$), HbA1c $\geq 6.5\%$ ($n = 859$), and history of DM or use of anti-diabetic medications ($n = 1218$). After exclusion, 18,504 men were included in the study. Participants provided written informed consent for the use of their health screening data for research. This study was reviewed and approved by the Institutional Review Board of Kangbuk Samsung Hospital after which the specific data required for this study were released by the data management group of KSHS after deleting participants' personal information.

Anthropometric and Laboratory Measurements

Medical assessment included a medical history, physical examination, fasting blood samples and an imaging study

for the assessment of CAC. Body mass index (BMI) was calculated as dividing weight (kg) by height squared (m^2). Smoking status was reported as never, past, or current. We measured blood pressure using standard mercury sphygmomanometers in the upper arm of the study populations in a seated position for at least 5 min and in a quiet and relaxed environment. Hypertension was diagnosed by the following criteria: systolic blood pressure (SBP) ≥ 140 or diastolic blood pressure (DBP) ≥ 90 , history of hypertension, or the use of antihypertensive agents. DM was diagnosed when subjects had one among a FPG ≥ 126 mg/dL, HbA1c $\geq 6.5\%$, a self-reported history of diabetes, or use of antidiabetic medications.

Blood samples were collected after an overnight fast. FPG was measured using hexokinase method (Hitachi Modulator D2400; Roche, Tokyo, Japan). Fasting serum insulin was measured by electrochemiluminescence immunoassay (Hitachi Modular E 170; Roche, Tokyo, Japan). Serum creatinine level was measured by the alkaline picrate (Jaffe) method. Serum calcium and phosphate were measured using a standard colorimetric method (Roche Diagnostics, Alameda, CA). Serum total cholesterol (TC) and triglycerides (TG) were measured by an enzymatic calorimetric test, low-density lipoprotein cholesterol (LDL-C) was measured by a homogeneous enzymatic calorimetric test, and high-density lipoprotein cholesterol (HDL-C) was measured by the selective inhibition method. Serum high-sensitivity C-reactive protein (hs-CRP) was measured using a nephelometric assay (BNII nephelometer, Dade Behring, Deerfield, IL). HbA1c was measured by immunoturbidimetric assay with a Cobra Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland) with a reference value of 4.4–6.4%. The methodology was aligned with the Diabetes Control and Complications Trial (DCCT) and National Glycohemoglobin Standardization Program (NGSP) standards (11). Intra-assay coefficient of variation (CV) was 2.3% and the inter-assay CV was 2.4%; both were within the NGSP acceptable limits (12).

Insulin resistance was evaluated by the HOMA-IR index as calculated by the following formula: (fasting insulin [uIU/mL] x fasting blood glucose [mmol/L])/22.5 (13). To evaluate the impact of insulin resistance on CAC in relation to HbA1c levels, subjects were grouped into HOMA-IR quartile and classified as insulin-sensitive (lowest quartile) or insulin-resistant (highest quartile).

Subjects were also grouped by HbA1c quartile (first quartile, HbA1c $\leq 5.4\%$ ($n = 4484$); second quartile, $5.4 \leq \text{HbA1c} \leq 5.6\%$ ($n = 5722$); third quartile, HbA1c = 5.7% ($n = 2737$); fourth quartile, $5.8 \leq \text{HbA1c} \leq 6.4\%$ [$n = 5561$]).

Measurement of Coronary Artery Calcium Score

CAC score was measured using a 64-slice multidetector computed tomography scanner (GE Healthcare, Tokyo,

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