A1C and Coronary Artery Calcification in Nondiabetic Men and Women

Yoosoo Chang, Kyung Eun Yun, Hyun-Suk Jung, Chan-Won Kim, Min-Jung Kwon, Eunju Sung, Seungho Ryu

Objective—This study aimed to examine the association between glycohemoglobin (A1C) and coronary artery calcification (CAC) in nondiabetic men and women without overt cardiovascular disease or diabetes mellitus after accounting for fasting glucose and traditional cardiovascular disease risk factors.

Approach and Results—A cross-sectional study was performed in 25,564 Korean adults (41.4±7.0 years) with no diabetes mellitus (fasting glucose, ≥7.0 mmol/L or a history of diabetes mellitus) and no clinically evident cardiovascular disease, who underwent a health checkup, including a cardiac computed tomography estimation of CAC scores and measurements of cardiovascular risk factors. The presence of CAC was defined as a CAC score >0; CAC was observed in 12.0% of men and 4.9% of women. Age-adjusted odds ratios (95% confidence interval) for CAC comparing A1C of 5.5% to 5.6%, 5.7% to 5.9%, and 6.0% to 6.4% with A1C <5.5% were 1.12 (0.99–1.28), 1.44 (1.27–1.63), and 1.63 (1.39–1.90) in men and 1.76 (0.96–3.25), 1.86 (1.05–3.29), and 3.09 (1.68–5.70) in women, respectively. After adjusting for potential confounders, the odds ratios (95% confidence interval) comparing A1C of 5.5% to 5.6%, 5.7% to 5.9%, and 6.0% to 6.4% with A1C of <5.5% were 1.04 (0.91–1.19), 1.21 (1.07–1.38), and 1.25 (1.05–1.48) in men and 1.75 (0.94–3.29), 1.59 (0.88–2.87), and 2.48 (1.29–4.74) in women, respectively. These associations persisted in subjects without any metabolic abnormalities, including fasting glucose ≥100 mg/dL.

Conclusions—A higher A1C level was found to have a modest and independent association with the subclinical coronary atherosclerosis, even in metabolically healthy individuals. (Arterioscler Thromb Vase Biol. 2013;33:2026-2031.)

Key Words: cardiovascular disease ■ coronary artery disease ■ glycohemoglobin A ■ Hb A1c ■ vascular calcification

Glycohemoglobin (A1C), a parameter for the 2- to 3-month average endogenous exposure to glucose, has high intraindividual reproducibility and can be determined in the nonfasting state. The diagnostic cut points of A1C for diabetes mellitus are mainly based on the established association between A1C and microvascular disease. There is increasing evidence, however, that the level of A1C predicts clinical cardiovascular disease (CVD) or cardiovascular mortality and this association, independent of fasting glucose, is observed even at levels of A1C below the cutoff point of 6.5%. To date, little data are available on the association between A1C and subclinical CVD measured by coronary artery calcification (CAC). Studies of subclinical CVD can provide complementary information to studies of clinical CVD outcomes by allowing the understanding of early stage of CVD, whereas studies of clinical CVD events are influenced by factors related to plaque rupture and thrombosis. CAC scoring using cardiac computed tomography is a sensitive method to identify the presence of subclinical atherosclerosis which is associated with future risk of CVD events. Thus, measuring CAC leads to a better understanding of the relationships between potential cardiovascular risk factors and subclinical coronary artery atherosclerosis.

Until now, a few studies have examined the association between A1C and CAC in asymptomatic nondiabetic population, with conflicting results. One study showed no association between A1C and calcified plaque using computed tomography angiography, whereas the Multi-Ethnic Study of Atherosclerosis (MESA) study showed a significant association between higher A1C <6.5% and the presence of CAC, although only in women. The association between A1C and CAC was not described among euglycemic participants defined as fasting glucose <100 mg/dL.
To our knowledge, there are no published studies examining the association between the level of A1C and CAC in euglycemic participants. Therefore, the aim of this study was to examine the association between A1C levels and CAC in nondiabetic men and women without overt CVD or diabetes mellitus after accounting for traditional CVD risk factors, as well as the fasting glucose level, and to examine whether this association remains in the euglycemic population with fasting glucose <100 mg/dL.

Materials and Methods

Materials and Methods are available in the online-only Supplement.

Results

The mean (±SD) age and the percentage of male participants were 41.4 (±7.0) years and 84.8%, respectively. The prevalences of current smokers, hypertension, and metabolic syndrome were 28.5%, 13.4%, and 18.1%, respectively.

Baseline characteristics of the study population, both overall and according to A1C categories, are shown in Table 1. Age, waist circumference, body mass index, fasting blood glucose, systolic and diastolic blood pressures, total cholesterol, triglycerides, low-density lipoprotein-cholesterol, homeostasis model assessment of insulin resistance, and

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall</th>
<th>&lt;5.5</th>
<th>5.5–5.6</th>
<th>5.7–5.9</th>
<th>6.0–6.4</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>25564</td>
<td>6350</td>
<td>7988</td>
<td>8608</td>
<td>2618</td>
<td></td>
</tr>
<tr>
<td>Age, y*</td>
<td>41.4 (7.0)</td>
<td>39.8 (6.5)</td>
<td>40.7 (6.6)</td>
<td>42.4 (7.2)</td>
<td>44.2 (7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, %</td>
<td>84.8</td>
<td>85.4</td>
<td>85.4</td>
<td>84.4</td>
<td>83.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>28.5</td>
<td>26.6</td>
<td>28.5</td>
<td>28.9</td>
<td>32.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol intake, %</td>
<td>28.6</td>
<td>29.2</td>
<td>28.5</td>
<td>28.1</td>
<td>29.0</td>
<td>0.38</td>
</tr>
<tr>
<td>Regular exercise, %</td>
<td>43.2</td>
<td>43.7</td>
<td>42.9</td>
<td>43.5</td>
<td>42.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Family history of DM, %</td>
<td>19.5</td>
<td>15.4</td>
<td>18.5</td>
<td>21.3</td>
<td>26.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of MI, %</td>
<td>3.5</td>
<td>3.4</td>
<td>3.7</td>
<td>3.4</td>
<td>4.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>18.1</td>
<td>10.4</td>
<td>14.5</td>
<td>21.3</td>
<td>37.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatty liver on ultrasound, %</td>
<td>42.7</td>
<td>32.0</td>
<td>38.7</td>
<td>47.9</td>
<td>63.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>13.4</td>
<td>11.2</td>
<td>12.2</td>
<td>13.9</td>
<td>20.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertensive medication use, %</td>
<td>7.0</td>
<td>4.9</td>
<td>5.7</td>
<td>8.2</td>
<td>12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-lowering medication use, %</td>
<td>1.4</td>
<td>0.6</td>
<td>1.1</td>
<td>1.9</td>
<td>2.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ALT indicates alanine aminotransferase; BP, blood pressure; CAC, coronary artery calcification; DM, diabetes mellitus; HDL-C, high-density lipoprotein-cholesterol; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein-cholesterol; and MI, myocardial infarction.

Data are *mean (SD); §median (interquartile range); or percentage.

†≥20 g of ethanol per day.

‡≥1 time per week.
high sensitivity C-reactive protein were associated positively, whereas high-density lipoprotein-cholesterol was associated inversely. Participants with elevated A1C levels were more likely to smoke, to take antihypertensive and lipid-lowering medications, and to have metabolic syndrome, fatty liver, hypertension, and a family history of diabetes mellitus.

Of the 25564 participants, 12.0% of men and 4.9% of women had a CAC score >0. Table 2 presents the associations between A1C categories and the prevalence of detectable CAC. Higher levels of A1C were progressively positively associated with the presence of CAC. The association of A1C with CAC was not modified by sex (P for interaction >0.05), but this association was more evident in women.

In age-adjusted models, the odds ratios (95% confidence interval) for CAC score >0 comparing A1C of 5.5% to 5.6%, 5.7% to 5.9%, and 6.0% to 6.4% with A1C <5.5% were 1.12 (0.99–1.28), 1.44 (1.27–1.63), and 1.63 (1.39–1.90) in men and 1.76 (0.96–3.25), 1.86 (1.05–3.29), and 3.09 (1.68–5.70) in women, respectively. After adjusting for age, smoking, alcohol intake, regular exercise, body mass index, family history of diabetes mellitus, and family history of myocardial infarction, A1C of 5.7% to 5.9% and 6.0% to 6.4% was significantly associated with an increased prevalence of CAC in both men and women. The association also persisted after adjusting further for total cholesterol, triglyceride, high-density lipoprotein-cholesterol, glucose, systolic and diastolic blood pressures, use of lipid-lowering medication, and use of antihypertensive medication comparing A1C of 6.0% to 6.4% with A1C of <5.5%: odds ratio of 1.25 (95% confidence interval, 1.05–1.48) in men and 2.48 (95% confidence interval, 1.29–4.74) in women.

Further, we examined the association between A1C categories and the prevalence of CAC in euglycemic subjects (Table I in the online-only Data Supplement). Even in this restricted population, the association remained significant in both men and women.

The associations between A1C categories and the prevalence of CAC were similar across subgroups of the study participants with no significant interactions with age, obesity, metabolic syndrome, smoking status, family history of heart disease, and family history of diabetes mellitus (Table 3). These results were effectively unchanged, even after analyses were restricted to participants without any metabolic syndrome components or to normal weight participants with body mass index between 18.5 and 22.9 kg/m².

### Discussion

This study demonstrates that higher A1C levels in the prediabetic range is associated with the prevalence of CAC as a marker for subclinical coronary artery disease in apparently healthy men and women without overt CVD and diabetes mellitus. Adjustment for potential confounders did not substantially change these associations. These findings are consistent with a previous study; while the previous results from MESA showed the significant association between A1C and CAC only in women but not in men, we found this association in both men and women. Furthermore, in this study, the association between higher A1C and CAC was qualitatively unchanged, even in participants with euglycemic range of a fasting glucose <100 mg/dL or in participants without any metabolic syndrome components. Our findings suggest that glycemia measured by A1C in the prediabetic range is independently associated with subclinical coronary artery disease. Previous studies showed that A1C level below the clinical cutoff for diabetes mellitus predicted clinical cardiovascular events. The present finding supports that higher A1C at baseline increases cardiovascular event, not through the development of diabetes mellitus during the follow-up period, but...
possibly through an association between hyperglycemia and atherosclerosis, even within the nondiabetic range.

To our knowledge, this is the first study to report the A1C and CAC association in apparently healthy, nondiabetic men and women with fasting glucose <100 mg/dL. In this population, CAC was present in much smaller proportions, only 10.9% of the overall population (12.0% of men and 4.9% of women), compared with 53.5% from the MESA study.6 Because the presence of coronary calcium increases with increasing age,10 this smaller prevalence of detectable CAC can be explained by age difference. Our study population was much younger than previous reports by ≈20 years and showed better metabolic parameters, all of which are associated with CAC.11 Even in this young, healthy population, a higher A1C level was found to have a modest and independent association with CAC.

In contrary to the previous MESA finding,6 we found that the prevalence of CAC was associated with A1C in both women and men. Another study conducted in a non diabetic population showed that A1C is a better predictor of CVD-related and coronary heart disease–related mortality than fasting or postprandial glucose levels in women but not in men.12 In contrary to previous studies with relatively limited power, the large sample size of the current increased the power to show the existing association between higher A1C and CAC as statistically significant, separately for men and women. Although this association between A1C and CAC was not significantly different by sex in our study, women showed a much steeper increase in the prevalence of CAC at A1C level of 6.0% to 6.4%, whereas men showed a gradually increasing pattern of CAC across A1C categories with earlier significant increase of CAC at lower A1C levels. Indeed, impaired fasting glucose and impaired glucose tolerance have been reported to differ by sex,13 with more women than men having impaired glucose tolerance, reflecting different sex-related physiological processes. A1C indicates the average endogenous exposure to glucose, partly including postprandial spikes in the blood glucose level, which has been independently related to CVD.14 Therefore, the association between A1C and CAC could be different between men and women. Further studies are needed to address the differing impact of hyperglycemia on CVD between men and women.

### Table 3. Associations Between Glycohemoglobin Category and Coronary Artery Calcification in Clinically Relevant Subgroups

<table>
<thead>
<tr>
<th>Glycohemoglobin Category, %</th>
<th>&lt;5.5</th>
<th>5.5–5.6</th>
<th>5.7–5.9</th>
<th>6.0–6.4</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≥45 (n=7537)</td>
<td>1.00 (reference)</td>
<td>1.19 (0.99–1.42)</td>
<td>1.28 (1.07–1.53)</td>
<td>1.46 (1.14–1.86)</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt;45 (n=18027)</td>
<td>1.00 (reference)</td>
<td>1.02 (0.86–1.23)</td>
<td>1.41 (1.19–1.67)</td>
<td>1.66 (1.35–2.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=20935)</td>
<td>1.00 (reference)</td>
<td>1.19 (1.04–1.37)</td>
<td>1.56 (1.36–1.78)</td>
<td>2.00 (1.66–2.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes (n=4619)</td>
<td>1.00 (reference)</td>
<td>1.06 (0.79–1.42)</td>
<td>1.49 (1.14–1.96)</td>
<td>1.81 (1.34–2.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Without any metabolic syndrome trait (n=8250)</td>
<td>1.00 (reference)</td>
<td>1.11 (0.87–1.40)</td>
<td>1.46 (1.15–1.85)</td>
<td>2.13 (1.43–3.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 (n=15100)</td>
<td>1.00 (reference)</td>
<td>1.22 (1.03–1.44)</td>
<td>1.60 (1.36–1.89)</td>
<td>2.13 (1.70–2.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥25 (n=10433)</td>
<td>1.00 (reference)</td>
<td>1.12 (0.93–1.35)</td>
<td>1.51 (1.26–1.80)</td>
<td>1.83 (1.48–2.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>18.5 to &lt;23 (n=7619)</td>
<td>1.00 (reference)</td>
<td>1.21 (0.95–1.55)</td>
<td>1.49 (1.17–1.89)</td>
<td>1.85 (1.29–2.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker (n=7295)</td>
<td>1.00 (reference)</td>
<td>1.23 (0.99–1.52)</td>
<td>1.55 (1.26–1.92)</td>
<td>1.60 (1.22–2.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ex-smoker (n=7515)</td>
<td>1.00 (reference)</td>
<td>1.08 (0.87–1.32)</td>
<td>1.34 (1.11–1.64)</td>
<td>2.02 (1.58–2.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonsmoker (n=10754)</td>
<td>1.00 (reference)</td>
<td>1.27 (1.01–1.59)</td>
<td>1.86 (1.49–2.32)</td>
<td>2.38 (1.79–3.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=24661)</td>
<td>1.00 (reference)</td>
<td>1.04 (0.91–1.19)</td>
<td>1.23 (1.08–1.39)</td>
<td>1.32 (1.12–1.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes (n=903)</td>
<td>1.00 (reference)</td>
<td>1.51 (0.84–2.74)</td>
<td>1.17 (0.64–2.13)</td>
<td>1.00 (0.46–2.17)</td>
<td>0.810</td>
</tr>
<tr>
<td>Family history of diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=20574)</td>
<td>1.00 (reference)</td>
<td>1.08 (0.93–1.24)</td>
<td>1.26 (1.10–1.45)</td>
<td>1.31 (1.09–1.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes (n=4990)</td>
<td>1.00 (reference)</td>
<td>1.02 (0.75–1.39)</td>
<td>1.08 (0.81–1.45)</td>
<td>1.30 (0.91–1.86)</td>
<td>0.145</td>
</tr>
</tbody>
</table>

Logistic regression models were used to estimate ORs and 95% CIs. Adjustment for age, smoking status, alcohol intake, regular exercise, family history of diabetes mellitus, family history of myocardial infarction, BMI, total cholesterol, triglyceride, HDL-C, glucose, systolic and diastolic blood pressures, lipid-lowering medication use, and antihypertensive medication use except each stratification variable.

BMI indicates body mass index; CIs, confidence intervals; HDL-C, high-density lipoprotein-cholesterol; and OR, odds ratios.
for example, oxidative stress and protein glycation of vessel walls. The accumulation of advanced glycosylation end products in tissues may adversely affect vessel walls and induce the release of inflammatory cytokines. Protein glycation, which is increased in diabetes mellitus, is closely linked to endothelial cell dysfunction, an early marker of atherosclerosis. A1C assessment might provide not only information on chronic hyperglycemia but also seems to reflect individual susceptibility to protein glycation.

Furthermore, a recent study has shown that expressions of osteoblastic marker, osteocalcin, increased in subjects with higher A1C, even in the prediabetic range. Osteocalcin expression by the circulating progenitor cells increased in patients with coronary atherosclerosis, and the endothelial progenitors with an osteogenic phenotype were able to produce calcification in vitro and are associated with coronary endothelial dysfunction. CAC is an active process and can be seen at all stages of atherosclerotic development. These aforementioned findings can explain the underlying mechanism of the significant association between A1C and CAC in our study. There are several limitations to this study. First, values of fasting glucose and A1C were based on single measurements and should be repeated to determine the individual’s status. However, A1C has good preanalytical stability and is not affected by acute perturbations (eg, stress, exercise, and smoking). If A1C was misclassified because of a single measurement, the association between A1C and CAC could be attenuated. Second, we did not measure impaired glucose tolerance by an oral glucose tolerance test and this could have misclassified some participants with unknown diabetes mellitus as having normal fasting glucose, impaired fasting glucose, or a prediabetic A1C state. About 2.6% of adults aged ≥20 years with fasting glucose in the nondiabetic range have undiagnosed diabetes mellitus on the basis of the 2-h glucose test. However, this proportion of misclassification might not affect overall finding. Further in this study, even in the euglycemic range defined as fasting glucose <100 mg/dL, adjusting for fasting glucose did not change our findings qualitatively, as well as quantitatively. Third, the cross-sectional design precluded the determination of causality, and because of the observational nature of our investigation, the possibility of residual confounding cannot be completely eliminated. Finally, our study population may not represent the general Korean population. The age- and sex-standardized prevalence of type 2 diabetes mellitus defined as having fasting serum glucose level of ≥126 mg/dL or the use of blood glucose lowering agents), hypertension, obesity (body mass index, ≥25 kg/m²), and current smoker were lower than that of the general population (7.3% versus 10.5%, 23.4% versus 29.1%, 30.8% versus 31.5%, and 17.5% versus 26.5%, respectively). Therefore, it is highly probable that our study subjects were healthier than the general Korean population. However, our study has several strengths. A large sample size made it possible to examine the association between higher A1C and CAC, with enough power, separately for men and women among a young, healthy population, although Asians may have a less frequent prevalence of coronary artery disease than the White population. Likewise, we were able to demonstrate these associations among various relevant subgroups after accounting for possible confounders.

These data provide further evidence that a higher A1C level has a modest and independent association with the subclinical coronary atherosclerosis in both men and women. The current cutoff for the diagnosis of diabetes mellitus may be inadequate to identify individuals who could benefit from preventive intervention of CVD.

Disclosures

None.

References


**Significance**

In a nondiabetic Korean population (n=25 564), higher A1C levels, but below the cutoff conventionally used for a diagnosis of diabetes mellitus, were found to have a modest and independent association with the subclinical coronary atherosclerosis (measured by the presence of coronary artery calcification using a 64-channel multidetector computed tomography) in both men and women and this association persisted even in metabolically healthy individuals. The current cutoff for the diagnosis of diabetes mellitus may be inadequate to identify individuals who could benefit from preventive intervention of cardiovascular disease.
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### Supplement Material

**Supplementary Table I. Associations between glycated hemoglobin category and coronary artery calcification by gender among euglycemic population (defined as fasting blood glucose (FBG) <100 mg/dl)**

<table>
<thead>
<tr>
<th>Glycated hemoglobin category (%)</th>
<th>Number of participants</th>
<th>Age -adjusted ORs (95% CIs)</th>
<th>Multivariate ORs(^a) (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.5</td>
<td>4,431</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>5.5-5.6</td>
<td>5,049</td>
<td>1.12 (0.96-1.29)</td>
<td>1.08 (0.93-1.25)</td>
</tr>
<tr>
<td>5.7-5.9</td>
<td>4,596</td>
<td>1.42 (1.23-1.63)</td>
<td>1.32 (1.15-1.53)</td>
</tr>
<tr>
<td>6.0-6.4</td>
<td>865</td>
<td>1.70 (1.37-2.12)</td>
<td>1.47 (1.18-1.83)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.5</td>
<td>853</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>5.5-5.6</td>
<td>1,043</td>
<td>1.61 (0.85-3.04)</td>
<td>1.63 (0.86-3.10)</td>
</tr>
<tr>
<td>5.7-5.9</td>
<td>1,098</td>
<td>1.65 (0.93-3.01)</td>
<td>1.67 (0.91-3.07)</td>
</tr>
<tr>
<td>6.0-6.4</td>
<td>273</td>
<td>3.17 (1.63-6.16)</td>
<td>2.87 (1.45-5.67)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td>&lt;0.001</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td><strong>(P) for interaction by gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Logistic regression models were used to estimate odds ratios (ORs) and 95 percent confidence intervals (95% CIs).

\(^a\) Model 1: adjustment for age, smoking status, alcohol intake, regular exercise, family history of diabetes, family history of myocardial infarction, and body mass index; model 2: model 1 plus adjustment for total cholesterol, triglyceride, high-density lipoprotein-cholesterol, glucose, systolic and diastolic blood pressure, lipid lowering medication use and anti-hypertensive medication use.
Materials and Methods

Study population

The study population consisted of examinees who underwent a cardiac CT estimation of CAC scores as part of a comprehensive health checkup at Health Screening Center of Kangbuk Samsung Hospital in Seoul and Suwon, South Korea from 2010 to 2011 (N=31,527), where all measurements were performed using identical equipment and standardized protocols. This type of screening examination is common in Korea. Additionally, in Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. Most of the participants were employees of various companies and local governmental organizations and their spouses and the remaining participants registered individually for the program.

Out of 31,527 participants, 5,963 were excluded for any of the following reasons: subjects with missing data on A1C or other covariates; subjects with diabetes mellitus defined as a fasting serum glucose ≥126 mg/dL, A1C ≥6.5%, a history of diabetes mellitus or the use of blood glucose lowering agents; subjects with a history of malignancy; and subjects with a history of cardiovascular disease. Because some individuals met more than one criterion for exclusion, the total number of eligible subjects for the study was 25,564 (Figure 1).

This study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital, which exempted the requirement for informed consent given the retrospective nature and anonymity of the data analyses.

Measurements

Data on medical history, medication use, health-related behaviors, physical measurements, and serum biochemical measurements were collected during the health examinations. Questions regarding alcohol intake included weekly frequency and the usual daily amount of
alcohol consumption. From the self-administered questionnaire data, we identified current smokers and accessed information on the weekly frequency of moderate- or vigorous-intensity physical activity, past medical history, medication use, and family history. Family history of diabetes mellitus or myocardial infarction was defined by diabetes mellitus or myocardial infarction in one or more first-degree relatives at any age. Body weight was measured in light clothing without shoes to the nearest 0.1 kilogram using a digital scale. Height was measured to the nearest 0.1 centimeter. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Trained nurses measured sitting blood pressure (BP) with standard mercury sphygmomanometers. The waist circumference was measured at the midpoint between the bottom of the rib cage and the top of the iliac crest to the nearest 0.1 cm with the subjects standing with weight equally distributed on both feet, arms at their sides, and head facing forward.

Blood samples were taken from the antecubital vein after at least a 10-hour fast. Serum levels of uric acids, total cholesterol, and triglyceride were determined using an enzymatic colorimetric assay; low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were directly measured using an homogeneous enzymatic colorimetric assay. Serum high sensitivity C-reactive protein (hsCRP) level was determined using a particle-enhanced immunoturbidimetric assay on a Modular Analytics P800 apparatus (Roche Diagnostics). Serum insulin level was measured using an electrochemiluminescence immunoassay on a Modular Analytics E170 apparatus (Roche Diagnostics) and serum fasting glucose level was measured using the hexokinase method on the Cobas Integra 800 apparatus (Roche Diagnostics; Rotkreuz, Switzerland). For determination of glucose level, serum was centrifuged within 30 after blood sampling. HbA1C determination using the Cobas Integra 800 (Roche Diagnostics, Rotkreuz, Switzerland) is based on the turbidimetric inhibition immunoassay for hemolyzed whole blood (reference range 4.4-6.4%). HbA1C measurements
were standardized to the reference method aligned with the Diabetes Control and Complications Trial and the National Glycohemoglobin Standardization Program standards. The intrassay coefficient of variation was 2.3% and interassay coefficient of variation was 2.4%, both of which are within the acceptance range of the aforementioned standardization program.  

All blood measures were analysed in the same laboratory with the same machines by the same trained staff using the same methodology. The Laboratory Medicine Department at Kangbuk Samsung Hospital in Seoul, Korea has been biannual accredited by the Korean Society of Laboratory Medicine (KSLM), and annual participate survey of the Korean Association of Quality Assurance for Clinical Laboratories (KAQACL) and the CAP (Collage of American Pathologists) Proficiency Testing.

Abdominal ultrasounds were performed using a Logic Q700 MR 3.5-MHz transducer (GE, Milwaukee, WI, USA) by 12 experienced radiologists who were unaware of the aims of the study. An ultrasonographic diagnosis of fatty liver was defined as the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma.  

Metabolic syndrome was defined as the presence of three or more ATP III criteria: 1) abdominal obesity (waist circumference ≥ 0.9 m in men and ≥ 0.85 m in women); 2) fasting blood glucose ≥100 mg/dL; 3) triglycerides ≥150 mg/dL; 4) HDL-C <40 mg/dL for men and <50 mg/dL for women; and 5) BP Ól30/85 mm Hg. Overall obesity was defined as BMI ≥25 kg/m², according to WHO Asia-Pacific guideline. Hypertension was defined as systolic BP Ól40 mmHg or diastolic BP Ól90 mmHg or the use of anti-hypertensive medication. Diabetes mellitus was defined as fasting serum glucose ≥126 mg/dL, A1C ≥6.5% or the use of blood glucose lowering agents. Insulin resistance was assessed with the Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) according to the following equation: [fasting
blood insulin (uU/ml) × fasting blood glucose (FBG) (mmol/l)] ÷ 22.5.

**Measurement of CAC by multidetector CT**

CT scans were performed with a Lightspeed VCT XTe-64 slice MDCT scanner (GE Healthcare, Tokyo, Japan) in both Seoul and Suwon centers using a same standard scanning protocol, which was 32*2.5-mm section collimation, 400 ms rotation time, 120 kV tube voltage, and 124 mAS (310 mA*0.4 second) tube current under ECG-gated dose modulation. The quantitative CAC scores were calculated as previously described by Agatston et al. The presence of CAC was defined as a CAC score >0.

A random sample of 60 patients (20 patients with CAC agatston score of zero, 20 patients with CAC agatston score of 1-99, and 20 patients with agatston score of 100 or greater) were re-read by the two technicians. The inter-observer reliability and the intra-observer reliability for CAC scores were both excellent (intraclass correlation coefficients of 0.99).

**Statistical analysis**

Baseline characteristics of the study population were calculated both overall and according to the categories of A1C values. There has been some disagreement over what A1C level should define prediabetes, and professional organizations have independently recommended at least three different cutoffs of 6.0%, 5.7%, and 5.5%. Therefore, in this study, A1C levels were categorized as <5.5%, 5.5-5.6%, 5.7-5.9%, and ≥6.0%. The distribution of continuous variables was evaluated and appropriate transformations were performed during analysis as needed. Odds ratios (ORs) were used to measure the association of the presence of coronary calcium with A1C categories. Logistic regression models were used to estimate ORs and 95% confidence intervals (CIs), after adjusting for potential confounders. The models were
initially adjusted for age, and then for smoking, alcohol intake, regular exercise, BMI, total cholesterol, triglyceride, HDL-C, glucose, systolic and diastolic BP, family history of diabetes, family history of myocardial infarction, the use of lipid lowering medication, and the use of anti-hypertensive medication. To determine linear trends of risk, a number of categories was used as a continuous variable and tested on each model.

Subgroup analyses was conducted according to sex, age groups (<45 vs. ≥45 years old), BMI (<25 vs. ≥25 kg/m²), metabolic syndrome (presence vs. absence), smoking status (current smoker or ex-smoker vs. noncurrent smoker); family history of heart disease (yes vs. no); and family history of diabetes (yes vs. no); and interaction by subgroups was tested.

The statistical analyses were done using STATA version 11.2 (StataCorp LP, College Station, TX, USA). All reported p values are two tailed with <0.05 considered statistically significant.
References


4. Executive summary of the third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii). *JAMA*. 2001;285:2486-2497


8. Jesudason DR, Dunstan K, Leong D, Wittert GA. Macrovascular risk and diagnostic criteria for type 2 diabetes: Implications for the use of fpg and hba(1c) for cost-


Figure legend

Figure 1. Flow diagram for the selection of study subjects

Participants who underwent a 64-slice cardiac computed tomography as part of a comprehensive health checkup at Health Screening Center of Kangbuk Samsung Hospital in Seoul and Suwon, South Korea from 2010 to 2011 (n=31,527)

Exclusions (n=5,963)
- Missing data on hba1c, glucose and important covariates (n=3,401)
- A history of malignancy (n=617)
- A history of cardiovascular disease (n=312)
- Diabetes mellitus (n=2,141)
  - Fasting serum glucose ≥6.99 mmol/l
  - HbA1c ≥6.5%
  - Current use of blood glucose-lowering agents
  - A history of diabetes mellitus

Apparently healthy, non-diabetic population included for the analysis (n=25,564)