Persistence or regression of prediabetes and coronary artery calcification among adults without diabetes

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Supplementary Tables

Table S1. Cross-sectional analysis; the absolute and relative prevalence of coronary artery calcification at the time of the first coronary artery calcium CT scan according to the changes in glycaemic status between the two visits: preceding the baseline (and first) CAC CT scan (CACS-1st) and at the first CAC CT scan (CACS-1st) (n=126,765)

Table S2. Prospective analysis; the association between changes in glycaemic status and ratios of 5-year progression rates of coronary artery calcium score between the first CAC CT scan and the subsequent CAC CT scan among participants with prediabetes (n=19,404)

Table S1. Cross-sectional analysis; the absolute and relative prevalence of coronary artery calcification at the time of the first coronary artery calcium CT scan according to the changes in glycaemic status between the two visits: preceding the baseline (and first) CAC CT scan (CACS-1st) and at the first CAC CT scan (CACS-1st) (n=126,765)

Glycemic status		Total number	CAC >0	(%)	Age- and sex-adjusted Coronary artery calcium score ratios (95% CI)	Multivariable-adjusted Coronary artery calcium score ratios*
visit 1	visit 2					
Normal	Normal	53,807	4,331	8.1	1.00 (reference)	1.00 (reference)
Normal	Prediabetes	18,952	2,139	11.3	1.42 (1.25-1.63)	1.02 (0.90-1.16)
Normal	Diabetes	51	8	15.7	2.97 (0.46-19.15	1.33 (0.22-8.11)
Prediabetes	Normal	14,627	1,534	10.5	1.30 (1.12-1.51)	1.11 (0.96-1.28)
Prediabetes	Prediabetes	37,857	6,264	16.6	2.17 (1.96-2.40)	1.31 (1.18-1.45)
Prediabetes	Diabetes	1,471	396	26.9	6.09 (4.49-8.26)	2.14 (1.59-2.90)

* Estimated from robust Tobit regression models used with natural log(CAC + 1) as the outcome. The multivariable model was adjusted for age, sex; Model 2: model 1 plus adjustment for center; year of screening exam, smoking status, alcohol intake, physical activity, education level, medication for hypertension, medication for dyslipidemia, BMI, LDL-C, and SBP at baseline.

Abbreviations: CAC, coronary artery calcification

Table S2. Prospective analysis; the association between changes in glycaemic status and ratios of 5-year progression rates of coronary artery calcium score between the first CAC CT scan and the subsequent CAC CT scan among participants with prediabetes (n=19,404)

Glycemic status		Ratio of 5-year CAC progression rate	
visit 1	visit 2	Age- and sex-adjusted model	Multivariable-adjusted model*
Prediabetes	Normal	0.93 (0.90−0.96)	0.93 (0.90−0.96)
Prediabetes	Prediabetes	1.00 (reference)	1.00 (reference)
Prediabetes	Diabetes	1.37 (1.06−1.77)	1.37 (1.06−1.77)

* 5-year CAC progression rates were estimated from mixed models with random intercepts and random slopes with natural log(CAC + 1) as the outcome and inverse probability weighting. The multivariable model included glycemic status change as well as smoking status, alcohol intake, physical activity, medication for dyslipidemia, medication for hypertension, BMI, LDL-C, and SBP as time-varying variables, and age at baseline, sex, center, year of screening examination, education level, and time-fixed variables.

Abbreviations: CAC, coronary artery calcification

Supplementary Methods and Discussion

Methods

Study population

More than 80% of the participants are employees, and their spouses, of local companies and government organizations. In South Korea, the "Industrial Safety and Health Law" requires all employees to undergo free health checks every year or every two years. The dataset collects sociodemographic information, medical history, and health-related behaviors provided by participants' self-administered questionnaires, anthropometric measurements, and laboratory measurements [1].

Data Collection

Smoking status was categorized as never, former, or current. The frequency of alcohol consumption and the amount of alcohol consumed per drinking day were recorded in standard units, which were used to estimate the average alcohol consumption per day. Participants were classified according to physical activity, assessed using the validated short-form Korean version of the International Physical Activity Questionnaire [2], as inactive, minimally active, or health-enhancing physical activity (HEPA). We defined HEPA as meeting either of two criteria: (1) vigorous intensity activity on ≥3 days/week accumulating ≥1500 metabolic equivalent (MET) min/week or (2) 7 days with any combination of walking, moderate intensity, or vigorous intensity activities, reaching at least 3000 MET min/week [2].

Obesity was defined as BMI ≥25 kg/m2 according to Asian-specific criteria [3]. Data on the use of medication for the treatment of hyperlipidaemia or hypercholesterolemia were obtained using a self-administered structured questionnaire. Similarly, data on the use of medication for the treatment of hypertension was obtained using the questionnaire. Fasting

serum lipid profiles, glycemic parameters, alanine transaminase (ALT), and high-sensitivity C-reactive protein (hs-CRP) levels were measured from blood samples obtained after at least 10 h of fasting. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as fasting blood insulin (mU/mL) × fasting blood glucose (mmol/L)/22.5.

Statistical analysis

The model was adjusted for potential confounders that might affect the relationship between changes in glycaemic status and CAC prevalence or progression. The confounding variables were defined as 1) being associated with exposure (changes in glycaemic status), 2) being associated with outcome (CAC prevalence or progression), and 3) not belonging to the causal pathway between exposure (changes in glycaemic status) and outcome (CAC prevalence or progression).

The mixed model can include participants with multiple observations (characterized by various measurements per participant, varying number of measures, and uneven intervals between measurements) in the analysis. Furthermore, since the mixed model does not require the assumption that the data are missing completely at random, it is less affected by selection bias when compared with generalised estimating equations or repeated-measures analysis of variance[4]. The mixed model can be used to measure the effect of time-varying data between baseline and follow-up data and be extended to non-Normal outcomes, while this is not possible with other methods[5].

Discussion

The group that progressed from normoglycemia to prediabetes showed a higher crude prevalence of CAC than the reference group; however, this association was not considered significant in the multivariable analysis. In the prospective analysis, progression from

normoglycemia to prediabetes was significantly and positively associated with CAC progression. Those newly diagnosed with prediabetes, having progressed from normoglycemia within a period of 1.5 years, might only have an extremely short-term exposure to hyperglycaemia that may not be enough to increase the risk of CAC. The group that progressed from normoglycemia to diabetes tended to have a higher prevalence of CAC; however, the number of patients in this group was relatively small to obtain reliable estimates of the association in both cross-sectional (n = 51) and prospective analyses (n = 2). Hence, future studies with a longer follow-up period are required to evaluate CAC progression and its consequences over time in each prediabetes subgroup.

Although CAC scoring is a useful measure for detecting subclinical atherosclerosis, the utility of routine CAC screening in asymptomatic individuals with a low CVD risk remains unclear. In most cases, CAC CT scans were available as part of the screening package contracted by the employer of the participant with the health screening centre. The employee can choose two specialised tests of 10 possible options at each examination. Because participants were recruited continuously in the study beginning in 2010, many of the participants recruited in more recent years have not been in the screening programme long enough to undergo a second CAC measurement. Accordingly, 68% of our study participants did not have information on follow-up CAC measurements. To correct for potential selection bias, we used inverse probability weights (IPWs) that reweight study participants; the participants who are similar to those lost to follow-up after the first coronary CT scan are assigned a higher weight[4]. All analyses reported are corrected for IPWs.

Reference

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