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

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Abstract

Objective: The effect of changes in glycemic status on subclinical atherosclerosis is uncertain. We assessed the association of persistence, regression or progression of prediabetes with coronary artery calcium score (CACS) as a measure of subclinical atherosclerosis.

Design: A cross-sectional study, comprising 126,765 adults, and longitudinal sub-study, comprising 40,622 adults (with baseline and at least one follow-up computed tomography scan to assess changes in CACS), were undertaken.

Methods: Changes in glycemic status over 1.5 years (interquartile range, 1.0–2.0) before the first CACS assessment were categorized according to six groups: persistent normoglycemia (reference), normoglycemia to prediabetes, normoglycemia to diabetes, prediabetes to normoglycemia, persistent prediabetes, and prediabetes to diabetes. Logistic regression was used to calculate the odds ratios (ORs) and 95% CIs for prevalent coronary artery calcification (CAC). Mixed models with random intercepts and random slopes were used to estimate 5-year CAC progression rates.

Results: Mean (SD) age was 41.3 (7.0) years (74.7% male) (n=126,765). Multivariable-adjusted OR for prevalent CAC was 1.12 (95% CI 1.07–1.18) for persistent prediabetes, 1.05 (0.98−1.13) for regression to normoglycemia, and 1.43 (95% CI 1.25–1.64) for progression from prediabetes to diabetes, compared with persistent normoglycemia. CAC progression increased significantly in all prediabetes groups. Multivariable-adjusted ratio of 5-year CAC progression rates was 1.19 (95% CI 1.16–1.22) (persistent prediabetes), 1.11 (1.07−1.14) (regression to normoglycemia) and 1.63 (95% CI 1.26−2.10) (progression from prediabetes to diabetes).

Conclusions: Unfavorable changes in glycemic status, including persistence of prediabetes or progression to diabetes from prediabetes, were associated with increased risk of CAC.

Significance Statement

We present the data from a very large cohort study showing for the first time that persistent prediabetes and progression from prediabetes to diabetes were significantly associated with a higher prevalence of coronary artery calcification (CAC) at baseline, and higher 5-year CAC progression rates over time. Compared to the groups with persistent prediabetes, those who reverted from prediabetes to normoglycemia had a significantly reduced 5-year progression rate of CAC. We suggest that reversion from prediabetes to normoglycemic could prevent the progression of atherosclerosis.

INTRODUCTION

The prevalence of prediabetes or hyperglycemia, defined as glycemic levels above normal but below the diabetes threshold, is increasing worldwide. It is estimated that prediabetes will affect more than 470 million people by 2030 [1], 70% of whom will eventually develop diabetes [2]. Prediabetes not only increases the risk of progression to diabetes, but also increases the risk of various adverse outcomes, including cardiovascular diseases (CVD) and all-cause mortality [3-6]. Prediabetes was suggested to cause CVD in a recent Mendelian randomization analysis study [7]. Considering the high prevalence of prediabetes, its potential to progress to diabetes, and its complications; additional attention and appropriate management of prediabetes is needed, to potentially reduce cardiovascular risk and other complications.

Pathophysiological evidence suggests that atherosclerotic changes occur before the clinical manifestation of diabetes [8]. A higher atherosclerotic burden and lipid-rich coronary plaques have been found in individuals with prediabetes [8, 9]. Additionally, prediabetic status has been associated with inflammation and vasoconstriction, which may promote atherosclerosis in the coronary arteries [10, 11]. Nevertheless, observational studies have reported inconsistent findings regarding the relationship between prediabetes and subclinical atherosclerosis, a potential precursor of subsequent CVD events [12-14]. While previous studies have also suggested that an unfavorable change in glycemic status or persistent prediabetes is significantly associated with an increased risk of CVD, such as risks of myocardial infarction [15, 16], stroke, and all-cause mortality in patients [16], it is currently uncertain whether changes in glycemic status are associated with changes in the progression of subclinical atherosclerosis among patients without diabetes.

Coronary artery calcification (CAC), which can be easily assessed by high-resolution computed tomography (CT), is an independent predictor of cardiovascular events and a useful indicator of subclinical coronary atherosclerosis [17, 18]. In addition, CAC progression over time is a significant predictor of mortality [19]. Therefore, in patients who did not have diabetes at baseline, we aimed to evaluate: a) the association between glycemic status change and baseline subclinical atherosclerosis determined by coronary artery calcium score (CACS) in a cross-sectional study and b), the association between glycemic status change and CACS progression over time (between baseline and follow-up CT scans) in a retrospective cohort study.

MATERIALS AND METHODS

Study population

The present large-scale study was conducted in a subsample of participants of the Kangbuk Samsung Health Study, for adults aged 18 years and older who underwent annual or biennial health screenings at the Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea [20] (see Supplemental Data).

This study included 129,350 men and women who underwent at least two visits for health examination between 2010 and 2019, including measurement of CACS via CT scans at the visit preceding the baseline (and first) CAC scan (CACS-1st) and at the first CAC scan (CACS-1st). Among the individuals, we excluded 1,910 participants for the following reasons: history of type 2 diabetes; family history of CVD; and missing covariates including values of glucose, hemoglobin A1, or body mass index (BMI). Some participants met more than one of the exclusion criteria, resulting in a total of 126,765 eligible participants (**Figure 1**). A timeline of the study design is shown in **Figure 2**. We also evaluated the prospective

association between changes in glycemic status and CAC progression. This analysis included all study participants who had at least one follow-up cardiac CT to measure the CACS until December 31, 2019 (n=40,622). Study participants have been recruited continuously since 2010, and half of the participants recruited in more recent years did not have a second CACS measurement included in the dataset used in the current study. Consequently, half of the participants (n=40,622) had a follow-up CACS and were included in the analysis of the prospective association between changes in glycemic status and CAC progression.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which waived the requirement for informed consent because we used only de-identified data routinely collected as part of health screening examinations (IRB No. 2022-02-001). All procedures used in this study adhered to the ethical principles of the Declaration of Helsinki for Medical Research Involving Human Subjects outlined in 2013.

Definition of diabetes, prediabetes, and normoglycemia

Diabetes mellitus was defined as fasting serum glucose levels ≥126 mg/dL, hemoglobin A1C (HbA1c) level ≥6.5% (48 mmol/mol), a history of diabetes, or the use of blood glucose-lowering agents. Impaired fasting glucose (IFG) was defined as fasting glucose levels ranging from 100 to 125 mg/dL. Participants with IFG or HbA1c levels of 5.7%−6.4% (39−47 mmol/mol) were classified as prediabetic [21]. Participants meeting all criteria of fasting glucose <100 mg/dL, HbA1c <5.7% (<39 mmol/mol), no history of diabetes, and no use of blood glucose-lowering agents were classified as having normoglycemia.

Participants were classified into six groups based on their glycemic status at two time points prior to the first (baseline) CT scan to assess CACS: 1) persistent normoglycemia (reference),

2) normoglycemia to prediabetes, 3) normoglycemia to diabetes, 4) prediabetes to normoglycemia, 5) persistent prediabetes, and 6) prediabetes to diabetes (**see Figure 2**).

Measurement of CAC by multidetector CT

CT scans were performed in both the Seoul and Suwon centers with a Lightspeed VCT XTe-64 slice MDCT scanner (GE Healthcare, Tokyo, Japan) using the standardized scanning protocol: 2.5-mm thickness, 400 ms rotation time, 120 kV tube voltage, and 124 mAS (310 mA × 0.4 s) tube current under ECG-gated dose modulation. CAC Agatston scores were calculated by summing the CACS of all foci in the epicardial coronary system [22]. The prevalence of CAC was defined as an Agatston score of >0 at the time of the first CT scan. The CAC progression was defined as any increase in CAC that consists of the following: a) conversion from CAC of 0 to detectable calcification and b) a CACS indicating progression among participants with a baseline CACS > 0. The CACS had good inter- and intra-observer reliabilities (intraclass correlation coefficient of 0.99) [20].

Data Collection

See Supplemental Data for data collection.

Statistical analysis

To assess the relationship between glycemic status category and CAC prevalence, a logistic regression model was used to estimate the odds ratios (ORs) with 95% CIs for the presence of CACS >0. Multivariable models were adjusted for age, sex, center, year of screening examination, smoking status, alcohol intake, physical activity, education level, medication for hypertension, lipid-lowering medication, BMI, LDL-C, and systolic blood pressure (SBP) (see Supplemental Data).

Furthermore, to account for changes in glycemic status and covariates during follow-up, we performed time-dependent analyses, using updated measurements of glycemic status change, and updated measurements of change in other conventional CVD risk factors (e.g. smoking status, alcohol intake, physical activity, lipid-lowering medication, medication for hypertension, BMI, LDL-C, SBP) as time-varying variables in the regression models.

We used a Tobit regression model for natural log (CACS + 1) with a Huber-White estimation of SEs in a sensitivity analysis with the CACS as a continuous variable [23]. By comparing the categories of change in glycemic status to the reference (persistent normoglycemia), Tobit models were used to estimate the CACS ratio and 95% CI across glycemic change categories. The estimated value of the Tobit model is expressed as an exponentiation. Tobit regression coefficient (CACS ratio) approximates the relative CACS increment comparing glycemic change categories to the reference category (persistent normoglycemia). For instance, a CACS of 1.50 is interpreted as a 50% increase in the CACS of a particular category compared to the reference category.

We further evaluated the prospective association between changes in glycemic status and CAC progression, with the second screening visit as the start of follow-up. We used linear mixed models with random intercepts and random slopes [24] to estimate CAC progression, adjusting for potential confounders (See Supplemental Data for selection of confounders).

We then estimated the 5-year change in the adjusted CACS for each category of glycemic change and compared these estimates to the 5-year change in the reference category (persistent normoglycemia). To account for potential differences between participants with a single CAC measurement and those with ≥2 CAC measurements, we performed an analysis using inverse probability weights for selection. We estimated the probability of having ≥2

CAC measurements using baseline characteristics and weighted each individual using the inverse of the predicted probability of having ≥2 CAC measurements in the analyses. Moreover, because the CACS were right-skewed, we performed the analysis after transforming the CACS into $\log_e$(CACS+1). The estimates from this model were then exponentiated to obtain the geometric means of CACS. Based on the glycemic change categories, the 5-year progression rate with 95% CI was estimated.

All statistical analyses were performed using Stata version 16.0 (StataCorp LP; College Station, TX, USA). All reported p values were two-sided, and comparisons were considered statistically significant at $p<0.05$.

RESULTS

The mean age of the study participants (n=126,765) at the first CAC visit was 41.3 years (SD 7.0), and 74.7% were men (**Table 1**). The two largest subgroups of short-term glycemic patterns were persistent normoglycemia (42.4%) and persistent prediabetes (29.9%). The interval between two visits for glycemic measurements was 1.5 years (interquartile range, 1.0–2.0). The overall prevalence of a CACS >0 was 11.6%. Individuals with persistent prediabetes or progression to worse glycemic status were more likely to have unfavorable cardiometabolic profiles and prevalent CAC than those with persistent normoglycemia.

Prevalent CAC by short-term change in glycaemic status: Cross-sectional analysis

We evaluated the prevalence of CAC, defined as an Agatston score > 0 at the time of the first CT scan according to the changes in glycaemic status between the first CAC CT scan and the prior visit. Specifically, the changes in glycaemic status indicate glycaemic status at the visit preceding the baseline [and first] CAC CT scan [CACS-1st] and the glycaemic status at the

first CAC CT scan [CACS-1st]) (Table 2). The prevalence rates of CAC were 12% and 43% higher for individuals with persistent prediabetes and for those who had progressed from prediabetes to diabetes, respectively, than that for those with persistent normoglycemia (reference group), after adjustment for cardiovascular risk factors and other confounders. There was a trend toward a higher prevalence of CAC in the group that changed its glycaemic status from prediabetes to normoglycemia, but this association was attenuated and no longer statistically significant (OR, 1.05; 95% CI, 0.98–1.13) after adjusting for confounders.

The group that progressed from normoglycemia to prediabetes or diabetes tended to have a higher prevalence of CAC; however, these associations did not reach statistical significance. In a sensitivity analysis using the Tobit regression model (**Table S1**) [25]with log (CACS + 1) as the dependent variable, the relationship between a change in glycemic status and the CACS was similarly observed.

CAC progression by short-term change in glycemic status: Prospective analysis

In the prospective analysis (Table 3), we further evaluated the CAC progression rates between the first CT scan and the follow-up CT scan according to the changes in the glycaemic status (as defined above) during a median follow-up of 4.2 years. The risks of 5-year CAC progression, estimated as the ratios of the 5-year CAC progression rates, were 19%, 63%, and 11% higher for individuals with persistent prediabetes, those who progressed from prediabetes to diabetes, and those who regressed from prediabetes to normoglycemia, compared with that for patients who had persistent normoglycemia (reference group), even after adjusting for changes in cardiovascular risk factors over time as time-varying covariates. However, compared with that of the persistent prediabetes group, the regression from prediabetes to normoglycemia group showed a 7% lower ratio of the 5-year CAC progression

rate (the ratio of the 5-year progression rates, 0.93; 95% CI 0.90−0.96) (**Table S2**)[25].

Only two patients progressed from normoglycemia to overt diabetes, and therefore insufficient to estimate significance.

DISCUSSION

In this large-scale study of over 126,000 young and middle-aged Korean adults without diabetes at the first visit, persistent prediabetes and progression from prediabetes to diabetes were both significantly associated with a higher prevalence of subclinical atherosclerosis measured using CACS (than that observed in the persistent normoglycemia group) in the cross-sectional analysis. In the subsample of participants with repeated CT measurements, the ratios of estimated 5-year CAC progression rates were significantly higher among people with persisting prediabetes than among those with persistent normoglycemia in the prospective analysis, even after adjusting for time-varying cardiovascular risk factors and other confounders. This key analysis allowed us to adjust for change over time in potential confounding cardiovascular risk factors between the baseline and follow-up. Importantly, these data showed that compared to the group with persistent prediabetes, those who reverted from prediabetes to normoglycemia had a significantly reduced 5-year progression rate of CAC, supporting the potential benefit of reversion from prediabetes to normoglycemia, in preventing the progression of atherosclerosis.

In our study, persistent prediabetes, in the period before the first CACS, was positively associated with both the presence of CAC on the first CT scan and CAC progression between baseline and follow-up CT scans compared to the group with persistent normoglycemia. Prediabetes or mildly increased glucose concentration is an important determinant of the

future risk of subclinical atherosclerosis, including CAC progression [26, 27]. Epidemiological evidence supports a continuous relationship between glycaemic parameters and CVD, similar to the relationship between cholesterol and blood pressure[28-30]. A longer duration of hyperglycemia has been linked to a higher risk of subclinical atherosclerosis [31, 32]. The cut-off for prediabetes can be arbitrarily drawn but is widely used in clinical practice. We classified the participants according to the definition of prediabetes widely used in clinical practice.[21] It is important to understand the clinical and prognostic implications for patients classified as having prediabetes, as many clinicians can make this diagnosis using the HbA1c measurement. Furthermore, the impact of persistent prediabetes on CAC over a period of time has not been clearly understood, with only a few studies examining this association. According to the CARDIA study, a long-term cohort study of approximately 3,600 black and white young adults without prediabetes or diabetes at baseline, the duration of prediabetes or diabetes estimated during a 25-year period was associated with the presence of CAC, highlighting that cumulative exposure to chronic hyperglycemia is associated with an increased risk of subclinical atherosclerosis [32].

In our study, individuals with progression from normoglycemia to prediabetes showed a higher risk of CAC progression than those with persistent normoglycemia during our relatively short-term follow-up period in which we assessed changes in glycemic status. Importantly, these data suggest that even over this relatively short period in which we assessed changes in glycemic status, there is evidence that exposure to prediabetes has an adverse effect on the progression of subclinical atherosclerosis. Our data therefore add to previous findings by revealing that prediabetes, even when persistent for a relatively short period, may lead to an increased risk of CAC progression.

Several previous studies have reported the impact of changes in glycemic status on CVD and all-cause mortality. However, few studies have specifically focused on the association between changes in glycemic status and the presence or progression of subclinical atherosclerosis. The Whitehall II cohort study found that reversion from 2-hour glucose-defined prediabetes to normoglycemia was associated with a decreased risk of CVD and mortality, although individuals reverting from fasting glucose- or HbA1c-defined prediabetes to normoglycemia were not at reduced risk of future CVD or death, compared to those with prediabetes, or those who progressed to diabetes [33]. These study results also supported the notion, raised over 20 years ago, that 2-hour glucose levels in the non-diabetic range, are a stronger determinant of all-cause and cardiovascular mortality, than fasting glucose or HbA1c levels [34]. However, in contrast to this notion, a recent prospective cohort study from China reported that reversion from fasting glucose-defined prediabetes to normoglycemia over 2 years was associated with a reduction in the risk of CVD and all-cause mortality, compared to a reference group who progressed to diabetes [35]. Taken together, these findings appear to indicate a benefit of reversion from prediabetes to normoglycemia (irrespective of the definition used) in CVD risk reduction, although prior to our study, no previous study has evaluated CAC progression as an outcome. We found that individuals who reverted from prediabetes (defined by fasting glucose or HbA1c concentrations) to normoglycemia had a lower risk of CAC progression than those with persistent prediabetes. Our study is therefore the first to document that normalization of the glycemic state from prediabetes may potentially help reduce the risk of subclinical atherosclerosis. While there is ongoing debate regarding the role of prediabetes on the risk of CVD [36], our findings lend further support to the importance of prediabetes management as a strategy for minimizing cardiovascular

complications. Therefore, we recommend that additional longitudinal cohort studies with longer follow-up duration are needed to confirm our findings.

There are some inherent limitations in our study. First, we could not use 2-hour glucose levels to define the glycemic status. Since our dataset consists of the participants' laboratory data obtained in the fasting state only, and 2-hour glucose levels were not available. Second, there was a lack of information on CAC density or volume in our database. A more refined measurement of CAC will provide a better understanding of the association between changes in the glycemic state and CAC progression. Third, even though a wide range of covariates at baseline and follow-up was adjusted in the models, there is an inherent possibility of residual confounding from the measured CVD risk factors and confounding from the unmeasured CVD risk factors. Fourth, the 1.5-year time interval (interquartile range, 1.0–2.0) between the two glycaemic status measurements to define the change in glycaemic status may be relatively short to determine these changes. However, according to a randomised controlled trial that assessed whether a lifestyle-intervention programme or the use of metformin would prevent or delay the development of diabetes, a reduction was observed in the mean fasting plasma glucose and HbA1c levels in the metformin and lifestyle-intervention groups in the first year of the trial[37]. Therefore, it is plausible that a 1.5-year interval between the two glycaemic status measurements in our study may be sufficient to observe a change in the risk of CAC progression. Finally, our findings may not be generalizable to populations of different ethnicities; and previous reports have noted ethnic differences in HbA1c trajectories [38]. Moreover, only one-third of the participants were included in our prospective analysis because the remainder did not undergo a second CAC CT scan. This could limit the generalisability of our findings (see supplemental data for more details).

However, the current study has important strengths. This study represents a large sample of Korean participants of a single ethnicity who have undergone detailed phenotyping with baseline and follow-up validated measurements of the CACS by high-resolution CT scanning. We also considered the change in CVD risk factors between the baseline and follow-up and took account of this in our analyses by adjusting for time-varying covariates in the analyses.

In conclusion, we have demonstrated that individuals with adverse changes in glycemic status, including persistent prediabetes or development of new prediabetes, over a 1−2-year period preceding a measurement of CACS, have an increased risk of subclinical atherosclerosis. Moreover, the risk of CAC progression for individuals in whom prediabetes regressed to normoglycemia was intermediate between that of the persistent normoglycemia and persistent prediabetes groups. Our findings consistently support prediabetes per se as an independent predictor for subclinical atherosclerosis and its progression.

Prediabetes is associated with CAC and the presence of CAC identifies subjects at increased risk of CVD [8, 9]. Assessment of progression of subclinical atherosclerosis using CACS is useful in clinical practice because measurement of CAC improves CVD risk prediction, over and above traditional cardiovascular risk factors [19]. However, prior to our study, it has been uncertain whether persistence or regression of prediabetes influences CAC progression. Herein, we provide evidence that persistent prediabetes represents a high risk state for atherosclerotic progression, whereas in contrast an improvement in glycaemia from prediabetes to normoglycemia, somewhat mitigates the risk of progression. Our findings emphasize that identifying and managing conventional cardiovascular risk factors in asymptomatic people with prediabetes could reduce progression to overt CVD.

Declaration of interest

All authors declare that they have no conflict of interest.

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Data Availability Statement

The data are not publicly available outside of the hospital because of Institutional Review Board restrictions (the data were not collected in a way that could be distributed widely). However, the analytical methods are available from the corresponding author upon request.

Authors' contributions

YCho, YChang, SR, and CDB planned, designed, and implemented the study, including quality assurance and control. SR analyzed the data and designed the study's analytical strategy. YChang and SR supervised field activities. YCho, SR, YChang, YK, IC, CWK, HJ, and HO conducted the literature review and prepared the Materials and Methods and Discussion sections of the text. YCho and YChang drafted the manuscript. All authors interpreted the results, and SR, SHW, and CDB contributed to the critical revisions of the manuscript. All authors approved the final version of this manuscript.

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Legends for Figures and Tables

Figure 1. Flow chart of study participants

Figure 2. Timeline of the study design. The glycaemic status such as normoglycaemia, prediabetes, or diabetes was defined (based on the fasting blood glucose or HbA1c level) at the visit preceding the baseline (and first) coronary artery calcium (CAC) CT scan (CACS-1st) and at the first CAC CT scan (CACS-1st). Changes in glycaemic status were then ascertained for each patient; the participants were divided into six groups: 1) persistent normoglycemia (reference), 2) normoglycemia to prediabetes, 3) normoglycemia to diabetes, 4) prediabetes to normoglycemia, 5) persistent prediabetes, and 6) prediabetes to diabetes. Accordingly, the associations were determined between the six groups for short-term change in glycaemic status and a) the baseline CAC scores (CACS-1st) (cross-sectional study) and b) CAC progression (the difference between CACS-1st and subsequent follow-up CT scan [if the latter were available; prospective study]). The median follow-up duration between the CAC CT scan at the first visit (CAC-1st) and last visit was 4.2 years (interquartile range, 2.8–6.0).

Table 1. General characteristics of study participants at visit 2 by glycemic status category at visits 1 and 2* (n=126,765)

Table 2. Cross-sectional analysis; the absolute and relative prevalence of coronary artery calcification^{a} 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 3. Prospective analysis; the association between changes in glycaemic status and 5-year progression rates of coronary artery calcium scorea between the first CAC CT scan and the subsequent CAC CT scan (n=40,622)