Significant Coronary Stenosis in Asymptomatic Chinese With Different Glycemic Status

Yu Xu, MD[1,2]
Yufang Bi, MD[1,2]
Mian Li, MD[2]
Tiange Wang, MD[2]
Kun Sun, MD[3]
Min Xu, MD[1,2]
Jieli Lu, MD[1,2]
Yi Yu, MD[3]
Xiaoying Li, MD, PHD[1,2]
Shenghan Lai, MD, MPH[4]
Weiqing Wang, MD[1,2]
Guang Ning, MD, PHD[1,2]

OBJECTIVE— To evaluate coronary artery stenosis in early diabetes or prediabetes asymptomatic of myocardial ischemia in community-dwelling Chinese adults.

RESEARCH DESIGN AND METHODS— Age- and sex-matched participants with normal glucose regulation (NGR), prediabetes, or diabetes diagnosed within 5 years, asymptomatic of coronary artery disease (CAD), were randomly selected from a community-dwelling Chinese population aged 40–60 years. Dual-source computed tomography coronary angiography was used to evaluate the existence and extent of coronary stenosis, which was considered significant if >50% narrowing of vessel lumen was detected.

RESULTS— After excluding uninterpretable segments attributable to motion artifacts, a total of 135 participants with NGR, 132 with prediabetes, and 134 with diabetes participated in data analysis. Significant coronary stenosis was detected in 10 (7.4%), 10 (7.6%), and 22 (16.4%) individuals with NGR, prediabetes, and diabetes, respectively (P for trend = 0.029). Diabetes, rather than prediabetes, was associated with a significant 2.34-fold elevated risk [odds ratio (OR) 2.34 (95% CI 1.01–5.43); P = 0.047] of significant coronary stenosis as compared with that associated with NGR. Levels of glucose evaluation were independently and significantly associated with risks of significant coronary stenosis in diabetes. Each 1-SD increase in fasting plasma glucose, 2-h postload plasma glucose, and HbA_{1c} conveyed 2.11-fold, 1.73-fold, and 1.81-fold higher risks of significant coronary stenosis, respectively, after adjustment for other conventional cardiovascular risk factors.

CONCLUSIONS—Using a noninvasive CAD diagnostic modality such as dual-source computed tomography coronary angiography, we detected a markedly elevated risk of significant coronary stenosis with early diabetes in asymptomatic Chinese adults.

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The prevalence of diabetes is increasing at an alarming rate and is projected to more than double in 2030 (1). China recently has been recognized as the world's new diabetes capital after a nationwide survey found a prevalence of 9.7% and an absolute number of 92.4 million diabetic adults in mainland China (2). People with diabetes have a two-fold to three-fold increase in cardiovascular risks compared with nondiabetic individuals (3,4). However, because of various causes including neurologic complications (5,6), myocardial ischemia including myocardial infarction is often silent in diabetic patients (7–9), which results in a delayed diagnosis, missed opportunities for treatment, and a poor prognosis (10). Therefore, early detection of coronary artery disease (CAD) before symptoms occur using a noninvasive diagnostic modality such as multislice computed tomography (CT) coronary artery angiography at a time when patients could benefit most from intensive medical intervention might be critical to reducing cardiovascular morbidity and mortality in diabetes.

Nevertheless, previous studies included subjects mostly at an advanced stage of their diabetes or consecutive patients who presented to the outpatient clinic (11–14). There have been limited data on coronary atherosclerosis in asymptomatic early diabetes or prediabetes. Therefore, the objective of this study was to estimate the prevalence of significant coronary stenosis, defined as >50% luminal narrowing measured by coronary CT angiography (CTA) and to compare that in normal glucose regulation (NGR) with that in early diabetes or prediabetes in community-dwelling Chinese adults without overt CAD symptoms.

RESEARCH DESIGN AND METHODS

Study population

The current study was nested in an ongoing community-based cohort study that investigated associations between glucose dysregulation and cardiovascular complications. The study design and protocol of baseline data collection of the cohort study were described previously (15). Briefly, all the permanent residents aged 40 years or older in Songnan community in Shanghai were invited to participate in a screening examination for cardiometabolic diseases. Among 10,185 participants, we randomly selected 5,250 subjects using a ratio of 1.0 [diabetes diagnosed previously or fasting plasma glucose (FPG) ≥7.0 mmol/L] to 1.2 (no previous diabetes and 5.6 ≤ FPG < 7.0 mmol/L) to 1.44 (no previous diabetes and FPG <5.6 mmol/L) and oversampling

From the [1]Key Laboratory for Endocrine and Metabolic Diseases of Ministry of Health, Rui-Jin Hospital, Shanghai Jiao-Tong University School of Medicine, E-Institute of Shanghai Universities, Shanghai, China; the [2]Shanghai Clinical Center for Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Department of Endocrinology and Metabolism, Rui-Jin Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai, China; [3]Xin-Hua Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai, China; and the [4]Department of Radiology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland.
Corresponding author: Guang Ning, gning@sibs.ac.cn.
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Y.X. and Y.B. contributed equally to this work.

people with lower glucose levels because they might have a lower participation rate than those with higher glucose levels, to undergo a much detailed and comprehensive evaluation including a standard 75-g oral glucose tolerance test. We then reclassified the participating 4,012 subjects (attendance rate, 76.4%) into NGR, prediabetes, and diabetes groups based on their diabetes history and FPG and 2-h postload plasma glucose (PPG) levels according to the 1999 World Health Organization criteria. There was no significant difference in age and sex distribution between those included and those not included in the cohort.

For the current study, we randomly selected 150 individuals from the diabetes group and 150 NGR group and 150 prediabetes group individuals matched for age and sex of diabetic participants, respectively, after excluding subjects with the following characteristics: *1*) age older than 60 years; *2*) having symptoms of CAD (chest pain or shortness of breath); *3*) having a history of cardiovascular diseases (myocardial infarction, unstable angina, percutaneous coronary intervention, or stroke); *4*) having abnormal Q waves on resting electrocardiogram (ECG); *5*) having a previous diagnosis of diabetes for >5 years; *6*) having impaired liver or renal function [alanine aminotransferease more than twice the upper limit of the normal range, serum creatinine level >133 μmol/L (1.5 mg/dL), or glomerular filtration rate <60 mL/min]; *7*) being pregnant or having significant medical comorbidities; *8*) having X-ray examination or CT scan within 1 year; *9*) having tachycardia (a heart rate >90 bpm) or arrhythmia such as atrial fibrillation on ECG that causes coronary artifacts during CTA examinations; and *10*) having a history of allergic reaction to iodine-containing contrast agent. Finally, a total of 420 individuals (attendance rate, 93%) participated in the current study.

The study protocol was approved by the Institutional Review Board of Rui-Jin Hospital and written informed consent was obtained from each participant after providing a full explanation of the protocol and procedure.

Data collection

During July 2009 and August 2010, all participants underwent a comprehensive examination including a detailed questionnaire, anthropometric measurements, biochemical evaluation, and CTA examination. Family history of CAD in first-degree relatives was recorded and history of chronic diseases and current use of medication were acquired. Smoking status was defined as current if a subject smoked cigarettes regularly in the past 6 months. The BMI was calculated as body weight in kilograms divided by body height in meters squared (kg/m^2). Blood pressure was measured in the nondominant arm in a seated position three times consecutively at 1-min intervals after at least 5 min of rest using an automated electronic device (OMRON Model HEM-752; Omron Company, Dalian, China). The last two readings were averaged for analysis. Participants without a previous diagnosis of diabetes underwent an oral glucose tolerance test. All participants were told to fast for at least 10 h before blood samples were collected.

Plasma glucose, serum triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol were measured using an autoanalyser (Beckman CX-7 Biochemical Autoanalyser, Beckman Coulter, Brea, CA). Hemoglobin A_{1c} (HbA_{1c}) was determined by high-performance liquid chromatography using the VARIANT II Hemoglobin Testing System (Bio-Rad Laboratories, Berkeley, CA) in a National Glycohemoglobin Standardization Program–certified laboratory of Shanghai Institute of Endocrine and Metabolic Diseases. Fasting serum insulin was measured by an electrochemiluminescence assay (Roche Diagnostics). The single-void first morning urine samples were collected to assess urinary albumin-to-creatinine ratio. Urinary albumin concentrations were determined by immunoturbidimetry and urinary creatinine concentrations were measured by a modified Jaffe method on an automatic analyzer (Beckman LX-20).

Diagnosis and definition

Diabetes was defined either by a previous diagnosis and contemporary antidiabetic medication or by levels of plasma glucose during oral glucose tolerance test according to the 1999 World Health Organization criteria. Prediabetes was defined as FPG ≥6.1 mmol/L and <7.0 mmol/L plus PPG <7.8 mmol/L or FPG <7.0 mmol/L plus PPG ≥7.8 mmol/L and <11.1 mmol/L in participants without a previous diagnosis of diabetes. The indexes of homeostasis model assessment (HOMA) of insulin resistance and HOMA β-cell function were calculated according to the formulas: HOMA of insulin resistance = fasting insulin concentration (mIU/L) × FPG (mmol/L) / 22.5; HOMA β-cell function = 20 × fasting insulin concentration (mIU/L)/[FPG (mmol/L) − 3.5]. Urinary albumin-to-creatinine ratio was calculated by dividing the urinary albumin concentrations by the urinary creatinine concentrations and expressed in milligrams per gram. Microalbuminuria was defined as an albumin-to-creatinine ratio between 30 and 300 mg/g.

CTA scan protocol

All examinations were performed on a dual-source CT scanner (SOMATOM Definition; Siemens Medical Solutions, Forchheim, Germany). None of the participants in the current study received β-blockers.

A standard retrospectively ECG-gated scanning protocol was applied, with 0.6-mm slice collimation, 330-ms gantry rotation time, 120-kV tube voltage, and a maximum tube current of 400 mAs/tube. All scans were performed using ECG-controlled tube current modulation. A bolus of 70 mL Iohexol injection (350 mg/mL iodine; Omnipaque; GE Healthcare Shanghai, Shanghai, China) was intravenously injected (4 mL/s) via an 18-gauge catheter placed in the antecubital vein, followed by a 40-mL saline chaser.

CTA image analysis

The CTA images were interpreted independently by an experienced senior radiologist, who was unaware of the clinical information of study participants, with an offline three-dimensional workstation (ADW 4.4; GE Healthcare, Waukesha, WI). Coronary arteries were divided into 15 segments according to the American Heart Association classification (16). Only segments with a diameter >1.5 mm were included for analysis. Furthermore, patients with uninterpretable segments attributable to motion artifacts were excluded. The presence of atherosclerotic plaques and luminal narrowing were evaluated using axial images and curved multiplanar reconstructions. Coronary plaques were considered when structures >1 mm^2 were detected within or adjacent to the coronary artery lumen, which could be clearly distinguished from vessel lumen and the surrounding pericardial tissue. Significant coronary stenosis was defined as >50% narrowing of vessel lumen.

Statistical analysis

Given an estimated response rate of 75%, we calculated that a sample size of 140 participants for each of the 3 groups was

needed to provide 90% power at a 2-tailed significance level of 0.05 to detect a difference from 5 to 20% of estimated prevalence of significant coronary stenosis assessed by CTA among the groups. All data were analyzed using SAS 9.2 (SAS Institute, Cary, NC). Continuous variables were presented as means ± SD or medians (interquartile ranges) for skewed variables. Categorical variables were shown in absolute numbers and percentages. Demographic and metabolic features and characteristics of coronary arteries in NGR, prediabetes, and diabetes were described and compared using ANOVA for continuous variables and logistic regression analysis for categorical variables, adjusted for age and sex. The study population was reclassified into groups of increasing coronary stenosis (participants without coronary stenosis, with <50% coronary stenosis, and with significant coronary stenosis). FPG, PPG, and HbA_{1c} levels and diabetes prevalence were then compared among these three groups.

To investigate the associations of various cardiometabolic factors with significant coronary stenosis, logistic regression models were used to assess the crude and multivariate-adjusted odds ratios (OR) of advanced age (age 53 years or older, representing the median cut-off value), female sex, family history of CAD, ACE inhibitor/angiotensin receptor blocker medication, current smoking, high school education or more, overweight/obesity, hypertension, high LDL, low HDL, prediabetes, and diabetes for risks of significant coronary stenosis. Variables for multivariate regression analysis were chosen as confounding factors depending on their clinical plausibility and external evidence such as previous research and previous beliefs, i.e., their well-recognized clinical relevance to both dysglycemia (the independent variable of interest) and cardiovascular diseases (significant coronary stenosis, the dependent variable) in this study, rather than internal statistical evidence from the data.

To further elucidate the differences between diabetic participants with or without significant coronary stenosis, general characteristics were compared. Crude and multivariate-adjusted ORs for significant coronary stenosis in diabetes by each 1-SD increase in levels of different glucose evaluations were calculated using logistic regression procedures.

Significance tests were two-tailed and $P < 0.05$ was considered statistically significant.

RESULTS—Nineteen (4.5%) patients with uninterpretable segments attributable to motion artifacts were excluded from analysis, which resulted in 135 with NGR, 132 with prediabetes, and 134 with diabetes participating for data analysis. Plaques were analyzed on a per-patient level.

General characteristics

Characteristics of the study population according to glycemic status are shown in Table 1. Generally, percentages of individuals with a family history of CAD, educated beyond high school level, or currently smoking were not significantly different among groups, whereas BMI, blood pressure, and triglycerides were elevated and HDL was decreased substantially in parallel with deteriorations in glucose levels, insulin sensitivity, and β-cell function. Medications using ACE inhibitors or angiotensin receptor blockers were basically similar among the three groups. Daily use of aspirin or statins was extremely rare in study participants. Only two individuals were using aspirin. One was in the NGR group and the other was in the prediabetes group, and both were without coronary plaques. Statins were used by only one individual who was diabetic and had nonsignificant coronary stenosis.

Subclinical CAD and glucose metabolism

As shown in Table 1, coronary plaques were found in 58 (43.0%) participants with NGR, in 77 (58.3%) with prediabetes, and in 74 (55.2%) with diabetes (*P* for

Table 1—*General characteristics of study population by glycemic status*

Characteristics	NGR	Prediabetes	Diabetes	*P* for trend
n	135	132	134	
Age (years)	52.3 ± 4.4	52.6 ± 4.2	52.8 ± 4.4	0.34
Male, *n* (%)	56 (41.5)	67 (50.8)	67 (50.0)	0.16
Family history of CAD, *n* (%)	22 (16.3)	20 (15.2)	26 (19.4)	0.41
High school education or more, *n* (%)	44 (32.6)	52 (39.4)	46 (34.3)	0.64
Current smoker, *n* (%)	40 (29.6)	43 (32.6)	46 (34.3)	0.82
BMI (kg/m^2)	24.6 ± 3.7	25.6 ± 3.2*	26.5 ± 3.7§	<0.0001
Systolic BP (mmHg)	125 ± 16	133 ± 18‡	139 ± 20§	<0.0001
Diastolic BP (mmHg)	76 ± 9	81 ± 10‡	83 ± 10§	<0.0001
Hypertension, *n* (%)	42 (31.1)	66 (50.0)†	79 (59.0)§	<0.0001
TC (mmol/L)	5.19 ± 1.04	5.07 ± 0.77	5.23 ± 1.03	0.59
LDL cholesterol (mmol/L)	2.39 ± 0.74	2.32 ± 0.63	2.41 ± 0.71	0.80
HDL cholesterol (mmol/L)	1.39 ± 0.33	1.35 ± 0.30	1.30 ± 0.27*	0.027
TG (mmol/L)	1.31 (0.96–1.95)	1.46 (1.10–2.35)	1.97 (1.42–3.13)§	<0.0001
FPG (mmol/L)	4.86 ± 0.47	5.27 ± 0.61*	7.26 ± 2.42§	<0.0001
PPG (mmol/L)	5.98 ± 0.96	8.84 ± 0.96§	14.52 ± 3.77§	<0.0001
HbA_{1c} (%)	5.80 ± 0.36	6.05 ± 0.44*	7.36 ± 1.50§	<0.0001
HOMA-IR	1.35 (0.90–1.93)	1.70 (1.08–2.48)†	2.80 (2.02–3.99)§	<0.0001
HOMA of β-cell function	91.4 (64.6–136.7)	85.8 (54.7–126.7)	56.5 (36.1–106.9)§	<0.0001
History of ACE inhibitor/ARB medication, *n* (%)	5 (3.7)	9 (6.8)	7 (5.2)	0.60
Any coronary plaques, *n* (%)	58 (43.0)	77 (58.3)*	74 (55.2)	0.081
Significant coronary stenosis, *n* (%)	10 (7.4)	10 (7.6)	22 (16.4)*	0.029

All comparisons were adjusted for age and sex. BP, blood pressure; TC, total cholesterol; TG, triglycerides; IR, insulin resistance; ARB, angiotensin receptor blocker. *$P < 0.05$ compared with NGR group. †$P < 0.01$ compared with NGR group. ‡$P < 0.001$ compared with NGR group. §$P < 0.0001$ compared with NGR group.

trend = 0.081), whereas plaques causing significant coronary stenosis were detected in 10 (7.4%), 10 (7.6%), and 22 (16.4%) individuals with NGR, prediabetes, and diabetes, respectively (P for trend = 0.029). Therefore, a similar prevalence of CAD detected by CTA was found in prediabetes and diabetes, and it was relatively higher than that in NGR; however, prevalence of significant coronary stenosis was doubled in diabetes and was substantially increased compared with that in NGR or prediabetes.

When participants were reclassified according to existence or extent of coronary stenosis, individuals with significant stenosis had dramatically elevated levels of FPG, PPG, and HbA_{1c} and had a significantly increased prevalence of diabetes compared with both groups of participants with <50% coronary stenosis and without stenosis after controlling for a variety of confounding factors (all $P < 0.05$; Fig. 1).

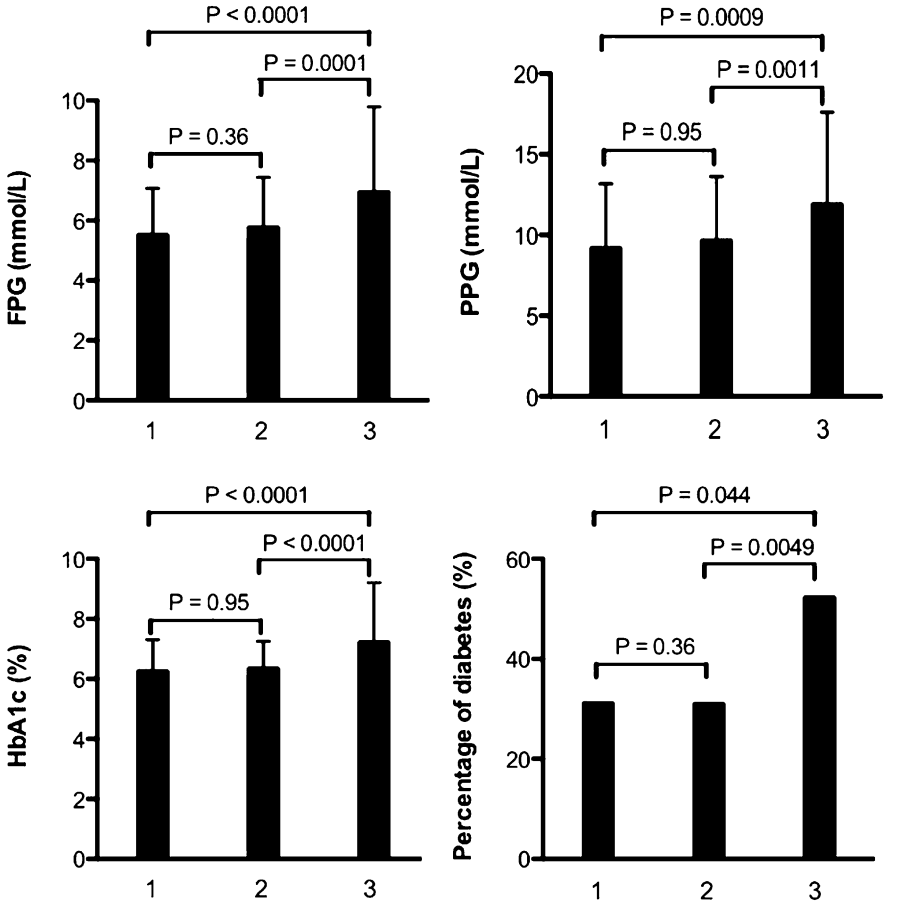

Figure 1—*Percentages of diabetes and levels of glucose evaluations in participants 1) without coronary stenosis, 2) with <50% coronary stenosis, and 3) with significant coronary stenosis, respectively. P values were adjusted for age, sex, family history of CAD, history of ACE inhibitor/angiotensin receptor blocker medication, smoking status, educational attainment, overweight or obesity, hypertension, high LDL cholesterol, and low HDL cholesterol.*

Cardiometabolic risk factors of significant coronary stenosis

Multivariate logistic regression analysis revealed few independent risk factors for significant coronary stenosis. Women were strongly protected from significant coronary stenosis [OR, 0.33 (95% CI, 0.14–0.81); $P = 0.016$; Table 2]. Prediabetes was not associated with an increased risk of significant coronary stenosis, whereas diabetes was associated with a significant 2.34-fold elevated risk [2.34 (1.01–5.43); $P = 0.047$] compared with NGR.

Significant coronary stenosis in diabetes

Among 134 patients with diabetes for <5 years, 22 (16.4%) had significant coronary stenosis. Diabetic individuals with significant coronary stenosis were more likely to be males and had more deteriorated glucose metabolism and β-cell function compared with those without significant coronary stenosis (Table 3). The presence of microalbuminuria tended to be increased in those with significant stenosis, but it failed to reach statistical significance. Among all cases of diabetes, 104 (77.6%) were newly diagnosed, but 14 (13.5%) already had significant coronary stenosis. Although newly diagnosed diabetes tended to occur more often in the group without significant coronary stenosis, the difference was not statistically significant.

In univariate and multivariate logistic analyses, glucose evaluation levels were independently and significantly associated with risks of significant coronary stenosis in diabetes. Each 1-SD increase in FPG, PPG, or HbA_{1c} conveyed 2.11-fold, 1.73-fold, or 1.81-fold higher risks of significant coronary stenosis, respectively, after controlling for other conventional cardiovascular risk factors (all $P < 0.05$; Table 4).

CONCLUSIONS—We used CTA, which is a noninvasive diagnostic modality, to characterize subclinical CAD in a community-dwelling adult population with NGR, prediabetes, or diabetes matched for age and sex. We found that although coronary stenosis was more prevalent in both prediabetes and diabetes, the risk of significant stenosis was only elevated in diabetes, despite a short duration of <5 years. Additionally, glucose evaluation levels were significantly and independently associated with risks of significant coronary stenosis in diabetic participants.

There has been a well-documented association between diabetes and cardiovascular diseases. Haffner et al. (17) reported that the presence of diabetes alone confers risk of cardiovascular mortality similar to that in nondiabetic individuals with a previous myocardial infarction. Heart disease is the most frequent cause of death in those with diabetes, accounting for 70% of all deaths (18). Coronary artery lesions in those with diabetes were often characterized as diffuse and multivessel, yet asymptomatic (19). In fact, silent myocardial ischemia is highly prevalent in the diabetic population. In the current study, 74 out of 134 diabetic patients (55.2%) were found to have a certain degree of coronary stenosis and 22 (16.4%) had significant stenosis, which was relatively low compared with most studies using CTA in asymptomatic patients with diabetes (11–14). The variation in prevalence may well reflect the important differences regarding population characteristics between studies. Those with higher prevalence rates of significant stenosis, ranging between ~26

Table 2—*Correlations of cardiometabolic factors with risks of significant coronary stenosis*

Independent variable	Significant coronary stenosis			
	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)*	*P*
Age 53 years or older	1.60 (0.84–3.06)	0.16	1.42 (0.71–2.87)	0.33
Female vs. male	0.41 (0.21–0.81)	0.0098	0.33 (0.14–0.81)	0.016
Family history of CAD	0.64 (0.24–1.68)	0.36	0.66 (0.24–1.82)	0.42
History of ACE inhibitor/ARB medication	1.46 (0.41–5.17)	0.56	1.36 (0.35–5.22)	0.66
Current smoker	1.34 (0.69–2.60)	0.39	0.60 (0.26–1.42)	0.24
High school education or more	0.90 (0.46–1.78)	0.77	0.97 (0.46–2.03)	0.92
Overweight or obesity	0.82 (0.43–1.56)	0.55	0.61 (0.30–1.26)	0.18
Hypertension	1.79 (0.93–3.43)	0.080	1.84 (0.87–3.88)	0.11
LDL cholesterol				
<2.6 mmol/L	1.00		1.00	
≥2.6 mmol/L	0.96 (0.49–1.86)	0.89	0.95 (0.46–1.95)	0.88
HDL cholesterol				
≥1.04 mmol/L (male); ≥1.29 mmol/L (female)	1.00		1.00	
<1.04 mmol/L (male); <1.29 mmol/L (female)	0.54 (0.23–1.26)	0.15	0.59 (0.24–1.45)	0.25
Glycemic status				
NGR	1.00		1.00	
Prediabetes	1.03 (0.41–2.55)	0.96	0.82 (0.32–2.14)	0.69
Diabetes	2.46 (1.12–5.41)	0.026	2.34 (1.01–5.43)	0.047

ARB, angiotensin receptor blocker. *ORs were adjusted for all the other independent variables within this table.

and ~41%, generally included a higher proportion of male participants (for example, 66% in the study by Rivera et al. (11) compared with 50% in the current study) and more patients with hypertension (69 vs. 59%), dyslipidemia (78 vs. 32%), or family history of CAD (30 vs. 19%). One study included patients with abnormal stress test results (13). Another important and more relevant fact is that participants in those studies had much longer duration of diabetes (mean duration, 7–10 years). Diabetes duration is thought to contribute significantly to CAD risks, and the Framingham Heart Study reported a 1.38-fold increased risk for CAD and a 1.86-fold higher risk for CAD death for each 10-year increase in diabetes duration (20). In previous studies, much attention has been given to diabetes of an advanced stage and CAD evaluation. There is a paucity of data on coronary artery stenosis in asymptomatic diabetes that has been diagnosed for a relatively short period of time. In the current study, a majority of individuals in the diabetes group were newly diagnosed (104/134; 77.6%) and the rest of diabetes cases were detected within 5 years. These diabetic participants were found to have a 2.34-fold increased risk for significant coronary stenosis compared with NGR. It is well-known that diabetes exists for several years before diagnosis, and thus an elevated risk of significant coronary stenosis in recently diagnosed diabetes may reflect a cumulative effect of glucose dysregulation that has been going on for years and for much longer than it had been noticed.

Moreover, among diabetic patients in this study, those with significant coronary stenosis had much higher glucose and HbA_{1c} levels than those without. Glucose evaluations, i.e., FPG, PPG, and HbA_{1c}, were found to be significant and independent risk markers for significant coronary stenosis in diabetes. Although deterioration of glucose homeostasis is reflective of a longer diabetes duration, elevated levels of glucose evaluations still were directly associated with increased risks of significant coronary stenosis in diabetes in that each 1-SD increment of glucose or HbA_{1c} level independently conveyed 1.73-fold to 2.11-fold elevated risks, adequately controlled for newly diagnosed cases and antidiabetic medications.

Participants with prediabetes were found to have a significantly higher prevalence of any coronary plaques but a similar prevalence of plaques causing >50% stenosis compared with NGR in this study. The close relationship between prediabetes and future CAD has been demonstrated by several studies (21–23). The enhanced atherogenic risk profile in prediabetes, such as higher BMI values and greater prevalence of hypertension, together with a prediabetes glucose level, may contribute to the elevated CAD prevalence in this study. Nevertheless, significant coronary stenosis as measured by CTA was not increased in prediabetes and was statistically lower than that in diabetes (7.6 vs. 16.4%; P = 0.027). Studies investigating biomarker trajectories leading to diabetes diagnosis reported modest changes in insulin sensitivity and secretion from normal to impaired glucose tolerance but substantial decreases during further progression to diabetes, leading to abrupt and steep increases in FPG and PPG levels during the few years (most likely 3 years) immediately before diagnosis (24,25). This is consistent with our findings on HOMA of insulin resistance and HOMA β-cell function in three groups with different glycemic status, and it might be one of the potential mechanisms of a markedly elevated risk for significant coronary stenosis in early diabetes compared with prediabetes. Noticeably, coronary plaques were found in 43.0% of NGR participants. In fact, despite glucose levels being within a normal range, 42% of these individuals were overweight or obese, 31% had hypertension, and 30% had dyslipidemia. Nearly 80% of these subjects had at least one cardiovascular risk factor, such as cigarette smoking, family history of CAD, overweight/obesity, hypertension, or dyslipidemia, indicating a noteworthy overall CAD risk profile in middle-aged Chinese adults residing in metropolitan cities such as Shanghai.

Multislice CT coronary angiography recently has emerged as a powerful imaging modality for noninvasive assessment of CAD. Except for high diagnostic accuracy for detecting CAD compared with the gold standard invasive coronary angiography (26–28), with a sensitivity of 89%, a specificity of 96%, and positive and negative predictive values of 78 and 98%, respectively (29), CTA also has been found useful in predicting future cardiac events in patients with known or suspected CAD (30–35). However, consistency is lacking regarding the use of CTA in asymptomatic subjects, particularly in high-risk asymptomatic patients, such as those with diabetes. The major concerns are unnecessary CT scan radiation, increased health care spending, and

Table 3—*Comparison of characteristics by coronary artery status in diabetes*

Characteristics	Diabetic participants		
	Without significant coronary stenosis	With significant coronary stenosis	*P*
n	112	22	
Age (years)	52.8 ± 4.4	52.9 ± 4.5	0.90
Male, *n* (%)	51 (45.5)	16 (72.7)	0.020
Family history of CAD, *n* (%)	23 (20.5)	3 (13.6)	0.60
Current smoker, *n* (%)	35 (31.3)	11 (50.0)	0.094
High school education or more, *n* (%)	40 (35.7)	6 (27.3)	0.41
BMI (kg/m^2)	26.6 ± 3.8	25.9 ± 3.5	0.60
Systolic BP (mmHg)	138 ± 19	144 ± 25	0.057
Diastolic BP (mmHg)	83 ± 9	85 ± 11	0.22
Hypertension, *n* (%)	66 (58.9)	13 (59.1)	0.75
TC (mmol/L)	5.21 ± 1.02	5.32 ± 1.08	0.30
LDL cholesterol (mmol/L)	2.41 ± 0.70	2.41 ± 0.78	0.61
HDL cholesterol (mmol/L)	1.31 ± 0.27	1.26 ± 0.26	0.74
TG (mmol/L)	1.91 (1.42–2.84)	2.67 (1.48–4.54)	0.15
FPG (mmol/L)	6.99 ± 2.21	8.65 ± 2.99	0.0034
PPG (mmol/L)	14.17 ± 3.56	16.31 ± 4.39	0.030
HbA_{1c} (%)	7.18 ± 1.25	8.30 ± 2.21	0.0028
HOMA-IR	2.83 (2.01–4.13)	2.38 (2.05–3.26)	0.86
HOMA of β-cell function	64.1 (37.0–117.4)	39.2 (20.3–56.8)	0.0016
Newly diagnosed diabetes, *n* (%)	90 (80.4)	14 (63.6)	0.12
Microalbuminuria, *n* (%)	11 (9.8)	4 (18.2)	0.11
Medication, *n* (%)			
ACE inhibitor/ARB	7 (6.3)	0	
Sulfonylureas	18 (16.1)	3 (13.6)	0.80
Metformin	9 (8.0)	4 (18.2)	0.22

All comparisons were adjusted for age and sex. BP, blood pressure; TC, total cholesterol; TG, triglycerides; IR, insulin resistance; ARB, angiotensin receptor blocker.

subsequent invasive cardiac procedures (36). However, recent advances in CTA technology, such as dual-source CT coronary artery angiography, have dramatically improved spatial and temporal resolution, leading to substantial improvement in image quality and significant reduction in radiation dose and use of contrast material (37).

Our findings may have important clinical implications. Currently, the American Diabetes Association consensus guidelines recommend CAD screening in diabetic individuals with cardiovascular symptoms (38). However, our study showed a markedly increased risk for the presence of significant coronary stenosis in asymptomatic patients with diabetes, even soon after its diagnosis. Furthermore, evidence has indicated similar frequencies of CAD in diabetic patients with and without angina symptoms (39,40). Therefore, cardiac testing for asymptomatic patients with diabetes should not be considered unwarranted, especially with the latest development in CT technology, which provides satisfactory cardiac images while reducing radiation dose. Meanwhile, although it could be somewhat premature to suggest that CTA examination should be routinely used for patients with recently diagnosed diabetes, our findings may imply that CTA screening should be used more aggressively in patients with diabetes, especially in those with additional risk factors such as dyslipidemia and hypertension. Nevertheless, whereas clinical effectiveness proves promising, cost-effectiveness is another important issue of concern before integrating CTA into patient care algorithms. It is possible that clinical outcomes may be sufficiently improved by use of CTA, justifying the substantially higher spending associated with its use. Therefore, longitudinal studies comparing costs of downstream testing and treatment of cardiovascular complications in diabetes with and without use of CTA are urgently needed.

Table 4—*Correlations of 1-SD increase in glucose evaluations with risks of significant coronary stenosis in diabetes*

Independent variable	Values of 1 SD	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)*	*P*
FPG (mmol/L)	2.42 mmol/L	1.71 (1.15–2.55)	0.0083	2.11 (1.29–3.45)	0.0029
PPG (mmol/L)	3.77 mmol/L	1.69 (1.08–2.64)	0.021	1.73 (1.06–2.81)	0.027
HbA_{1c} (%)	1.50%	1.83 (1.21–2.76)	0.0042	1.81 (1.17–2.81)	0.0080

*Adjusted for age, sex, family history of CAD, smoking status, educational attainment, newly diagnosed diabetes, antidiabetes treatment, overweight or obesity, hypertension, high LDL cholesterol, and low HDL cholesterol.

Despite the findings and the clinical implications for CAD management in asymptomatic early diabetes, this study suffers from several important limitations. First, the sample size was relatively small and thus did not allow separate analyses by sex or stratification by cardiovascular risks and did not take menopause status into account. Second, although participants with NGR, prediabetes, or diabetes were well-matched for age and sex, other important CAD risk factors such as hypertension were not considered when selecting participants. Therefore, a better-matched study population should have been used. Third, coronary stenosis was classified as <50% or ≥50% in this study, rather than a much detailed quantification to include severe stenosis, which is ≥75% narrowing of coronary artery lumen and is highly urgent for clinical intervention. Moreover, although many other cardiovascular risk factors such as smoking, hypertension, and dyslipidemia were adjusted for correlation of glucose dysregulation with significant coronary stenosis in the multivariate analyses, some residual or undetected confounding could not be ruled out.

In conclusion, we used noninvasive diagnostic CTA to anatomically assess subclinical CAD in middle-aged community-dwelling Chinese adults with different glycemic status. We detected a markedly increased risk of significant coronary stenosis in early diabetes without clinical manifestation of myocardial ischemia. Although prediabetes is thought to be predictive of future cardiac events, it was not

found to be associated with a higher risk of significant coronary stenosis. Follow-up studies are needed to investigate the long-term cardiovascular outcomes of CTA-confirmed subclinical atherosclerosis in patients with diabetes.

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Y.X. conceived and designed the study, analyzed and interpreted data, drafted the article, performed critical revision for important intellectual content, provided final approval of the article, provided statistical expertise, and collected and assembled data. Y.B. and W.W. conceived and designed the study, analyzed and interpreted data, drafted the article, performed critical revision for important intellectual content, provided final approval of the article, and collected and assembled data. M.L. and T.W. analyzed and interpreted data, drafted the article, provided final approval of the article, provided statistical expertise, and collected and assembled data. J.Z. analyzed and interpreted data, provided final approval of the article, and collected and assembled data. M.X. drafted the article, performed critical revision for important intellectual content, provided final approval of the article, and collected and assembled data. J.L. drafted the article, performed critical revision for important intellectual content, and provided final approval of the article. Y.C. analyzed and interpreted data, performed critical revision for important intellectual content, provided final approval of the article, and collected and assembled data. X.L. analyzed and interpreted data, performed critical revision for important intellectual content, and provided final approval of the article. S.L. conceived and designed the study, analyzed and interpreted data, performed critical revision for important intellectual content, provided final approval of the article, and provided statistical expertise. G.N. conceived and designed the study, analyzed and interpreted data, performed critical revision for important intellectual content, and provided final approval of the article. G.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
2. Yang W, Lu J, Weng J, et al.; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. N Engl J Med 2010;362:1090–1101
3. Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. Diabetes 1974;23:105–111
4. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979;241:2035–2038
5. Niakan E, Harati Y, Rolak LA, Comstock JP, Rokey R. Silent myocardial infarction and diabetic cardiovascular autonomic neuropathy. Arch Intern Med 1986;146:2229–2230
6. Wackers FJ, Young LH, Inzucchi SE, et al.; Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care 2004;27:1954–1961
7. Bradley RF, Schonfeld A. Diminished pain in diabetic patients with acute myocardial infarction. Geriatrics 1962;17:322–326
8. Cabin HS, Roberts WC. Quantitative comparison of extent of coronary narrowing and size of healed myocardial infarct in 33 necropsy patients with clinically recognized and in 28 with clinically unrecognized ("silent") previous acute myocardial infarction. Am J Cardiol 1982;50:677–681
9. Scheidt-Nave C, Barrett-Connor E, Wingard DL. Resting electrocardiographic abnormalities suggestive of asymptomatic ischemic heart disease associated with non-insulin-dependent diabetes mellitus in a defined population. Circulation 1990;81:899–906
10. Valensi P, Pariès J, Brulport-Cerisier V, et al. Predictive value of silent myocardial ischemia for cadiac events in diabetic patients: influence of age in a French multicenter study. Diabetes Care 2005;28:2722–2727
11. Rivera JJ, Nasir K, Choi EK, et al. Detection of occult coronary artery disease in asymptomatic individuals with diabetes mellitus using non-invasive cardiac angiography. Atherosclerosis 2009;203:442–448
12. Iwasaki K, Matsumoto T, Aono H, Furukawa H, Samukawa M. Prevalence of subclinical atherosclerosis in asymptomatic diabetic patients by 64-slice computed tomography. Coron Artery Dis 2008;19:195–201
13. Zeina AR, Odeh M, Rosenschein U, Zaid G, Barmeir E. Coronary artery disease among asymptomatic diabetic and non-diabetic patients undergoing coronary computed tomography angiography. Coron Artery Dis 2008;19:37–41
14. Sassa S, Shimada K, Yoshida K, Tanaka H, Jissho S, Yoshikawa J. Comparison of 64-slice multi-detector computed tomography coronary angiography between asymptomatic, type 2 diabetes mellitus and impaired glucose tolerance patients. J Cardiol 2008;52:133–139
15. Ning G, Bi Y, Wang T, et al. Relationship of urinary bisphenol A concentration to risk for prevalent type 2 diabetes in Chinese adults: a cross-sectional analysis. Ann Intern Med 2011;155:368–374
16. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975;51(Suppl):5–40
17. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234
18. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. Diabetes Care 1998;21:1138–1145
19. Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Circulation 1996;94:1818–1825
20. Fox CS, Sullivan L, D'Agostino RB Sr, Wilson PW; Framingham Heart Study. The significant effect of diabetes duration on coronary heart disease mortality: the Framingham Heart Study. Diabetes Care 2004;27:704–708
21. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161:397–405
22. Barr EL, Zimmet PZ, Welborn TA, et al. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation 2007;116:151–157
23. Barr EL, Boyko EJ, Zimmet PZ, Wolfe R, Tonkin AM, Shaw JE. Continuous relationships between non-diabetic hyperglycaemia and both cardiovascular disease and all-cause mortality: the Australian Diabetes,

Obesity, and Lifestyle (AusDiab) study. Diabetologia 2009;52:415–424
24. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet 2009;373:2215–2221
25. Ferrannini E, Nannipieri M, Williams K, Gonzales C, Haffner SM, Stern MP. Mode of onset of type 2 diabetes from normal or impaired glucose tolerance. Diabetes 2004;53:160–165
26. Hoffmann MH, Shi H, Schmitz BL, et al. Noninvasive coronary angiography with multislice computed tomography. JAMA 2005;293:2471–2478
27. Abdulla J, Abildstrom SZ, Gotzsche O, Christensen E, Kober L, Torp-Pedersen C. 64-multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: a systematic review and meta-analysis. Eur Heart J 2007;28:3042–3050
28. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324–2336
29. Schroeder S, Achenbach S, Bengel F, et al.; Working Group Nuclear Cardiology and Cardiac CT; European Society of Cardiology; European Council of Nuclear Cardiology. Cardiac computed tomography: indications, applications, limitations, and training requirements: report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. Eur Heart J 2008;29:531–556
30. Pundziute G, Schuijf JD, Jukema JW, et al. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. J Am Coll Cardiol 2007;49:62–70
31. Carrigan TP, Nair D, Schoenhagen P, et al. Prognostic utility of 64-slice computed tomography in patients with suspected but no documented coronary artery disease. Eur Heart J 2009;30:362–371
32. Hadamitzky M, Freissmuth B, Meyer T, et al. Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease. JACC Cardiovasc Imaging 2009;2:404–411
33. Rubinshtein R, Halon DA, Gaspar T, Peled N, Lewis BS. Cardiac computed tomographic angiography for risk stratification and prediction of late cardiovascular outcome events in patients with a chest pain syndrome. Int J Cardiol 2009;137:108–115
34. van Werkhoven JM, Schuijf JD, Gaemperli O, et al. Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. J Am Coll Cardiol 2009;53:623–632
35. Chow BJ, Wells GA, Chen L, et al. Prognostic value of 64-slice cardiac computed tomography severity of coronary artery disease, coronary atherosclerosis, and left ventricular ejection fraction. J Am Coll Cardiol 2010;55:1017–1028
36. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. JAMA 2011;306:2128–2136
37. Achenbach S, Ropers U, Kuettner A, et al. Randomized comparison of 64-slice single- and dual-source computed tomography coronary angiography for the detection of coronary artery disease. JACC Cardiovasc Imaging 2008;1:177–186
38. American Diabetes Association. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10-11 February 1998, Miami, Florida. Diabetes Care 1998;21:1551–1559
39. Zellweger MJ, Hachamovitch R, Kang X, et al. Prognostic relevance of symptoms versus objective evidence of coronary artery disease in diabetic patients. Eur Heart J 2004;25:543–550
40. Miller TD, Rajagopalan N, Hodge DO, Frye RL, Gibbons RJ. Yield of stress single-photon emission computed tomography in asymptomatic patients with diabetes. Am Heart J 2004;147:890–896