Clinical Research

Coronary artery disease in Chinese adults with type 2 diabetes mellitus estimated by electron beam computed tomography and electron beam computed tomography angiography

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Objective To assess the prevalence and risk of coronary artery disease (CAD) in Chinese adults with type 2 diabetes mellitus (T2DM) using electron beam computed tomography (EBCT) and EBCT angiography (EBCTA).

Methods: Ninety-four cases were enrolled in this study including diabetes (n=28), impaired glucose tolerance (IGT, n=30), coronary heart disease (CHD, n=11), and control (n=25). Cardiac EBCT plain scanning and EBCTA were performed on all of these subjects to evaluate coronary artery calcification (CAC) scores, and number of segments of stenosed coronary arteries. Both CAC and/or coronary artery stenosis were defined as patients with coronary artery lesions (CAL).

Results CAC scores were not different with the control, diabetes, IGT, or CHD (P>0.05) groups. Compared to control (0.520±1.295), more stenosed coronary arteries segments (P<0.05) were detected in diabetes (2.964±1.915), IGT (2.200±2.024), and CHD (2.273±1.679). Number of stenosed artery segments were correlated with age (r=0.215, P=0.019), postprandial glucose (r=0.224, P=0.015), total cholesterol (r=0.323, P=0.000), and duration of diabetes (r=0.208, P=0.004). The incidences of CAL in diabetes (96.43%), IGT (93.33%), and CHD (90.91%) was substantially higher than that in normal control (56.00%, P<0.01).

The odds ratio of CAL associated with having diabetes was estimated to be 7.514 (95% CI: 1.885-63.778).

Conclusions Coronary artery lesions are prevalent in Chinese adults with type 2 diabetes, implying a high CAD risk. EBCTA holds potential in depicting the details of CAL and can be used to track the progression of CAD in diabetes patients.

Key Words diabetes; coronary artery calcification; coronary artery stenosis; electron-beam computed tomography (EBCT)

Introduction

Diabetes mellitus is currently recognized as an equivalent to cardiovascular diseases. It has been confirmed that the mortality from cardiovascular complications in patients with type 2 diabetes is 2- to 4-fold higher than those without diabetes. It also has been reported that the 7-year cardiovascular mortality rate among patients with type 2 diabetes without a prior history of myocardial infarction is as high as that in non-diabetic patients with previous infarction. However, the severity of coronary artery disease (CAD) in type 2 diabetes differs in accordance with ethnicity/race and gender. Araneta et al. compared EBCT-defined coronary artery calcification (CAC) in Filipinos and white women without known cardiovascular disease. They found that Filipinos had no excess of subclinical atherosclerosis despite their significantly higher prevalence of type 2 diabetes, metabolic syndrome, hypertension, and visceral adiposity. Karter et al. found that adjusted hazard ratios (relative to that of whites) were lower for Asians and Latinos for MI and CHF. Currently, few studies have described CAD among Chinese with elevated T2DM prevalence. This study shows the value of assessing the prevalence and hazard of CAD respectively in Chinese diabetes patients.

In the past, the main examination method for estimating the stabilization or regression of CAD was invasive angiography. In recent years, CAC has been widely accepted as a marker of atherosclerotic burden. As a result, EBCT and multislice computed tomography (MSCT), new techniques for CAC examination, have been increasingly employed in clinics for its non-invasiveness and repeatability. Coronary EBCT angiography (EBCTA) and MSCT angiography (MSCTA) appear to have more advantages in evaluating coronary anatomy or demonstrating both the coronary lumen and the soft plaque attached to the artery wall. It was reported that the sensitivity and specificity of EBCTA for identification of coronary artery stenosis was 73-92% and 79-95%, respectively.

In this study, cardiac EBCT scanning and EBCTA were
selected to retrospectively investigate coronary artery disease in Chinese asymptomatic patients with type 2 diabetes. In addition, the data were analyzed to assess the risks of CAD in this population and to evaluate the roles of EBCT and EBCTA in estimation of CAD, with the wish to find potential cardiovascular events in asymptomatic type 2 diabetes Chinese patients.

Research design and methods

Patient selection
A total of 94 consecutive subjects aged 36-78 years were enrolled according to the history, physical and laboratory examinations of inpatients (from January, 2002 to June, 2004) at the Department of Geriatrics in Xijing Hospital. Among 58 patients with abnormal blood glucose and without history of coronary heart disease (CHD) (49 males and 9 females, aged from 40 to 67). 30 patients had impaired glucose tolerance (IGT), and 28 patients had diabetes with duration of diabetes of 10.2±4.7 years. Eleven cases (9 males and 2 females, aged 41 to 78 years) had CHD. In addition, 25 normal blood glucose subjects (22 males, 3 females, aged 36 to 75 years) who had no history of diabetes and CHD were selected as controls. The inclusion criteria included: patients with IGT or type 2 diabetes as defined by WHO in 1985; all patients with CHD as defined according to the report of the Joint International Society and Federation of Cardiology/World Health Organization Task Force on the standardization of clinical nomenclature and criteria for diagnosis of ischemic heart disease in 1991; all of them were confirmed by invasive coronary angiography. Exclusion criteria were: 1) patients with type 1 diabetes, and 2) patients with severe systematic diseases. The protocols were approved by an institutional review board and informed consent was obtained from all patients.

Laboratory examinations
All patients underwent the standard 75g oral glucose tolerance test (OGTT). Triglyceride, total cholesterol, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were determined after a minimum 8-hour fast in the Clinical Research Laboratory of Xijing Hospital. Plasma glucose was measured by the glucose-oxidase method. Fasting plasma triglyceride, total cholesterol, and HDL-C were measured by the enzymatic method. LDL-C was calculated from Friedewald’s formula.

EBCT scanning
A C-150 XP electron-beam CT scanner (Imatron Inc, USA) was used to perform the cardiac EBCT single slice mode plain scanning and contrast-enhanced scanning (EBCTA) described as standardized protocol. Forty to fifty cross-sectional images from 2 cm below trachea bifurcation to cardiac apex were acquired simultaneously with the scanner (slice thickness: 3 mm; table increment: 2 mm; acquisition time: 0.1 sec/slice) after every other heart beat at 40% of the R-R interval. A bolus of 100-150 ml of non-ion contrast agent (Omnipaque 300) was injected via the ulnar vein at a rate of 3.0-4.0 ml/s. A delay equal to the contrast media transit time (15 to 20 sec, mean 19±4) was maintained between the initiation of injection of the contrast agent and the acquisition of the first image. The acquisition of the images was performed with the onset of breath-holding for 30-40 sec according to the patient’s basal heart rate.

Estimation of CAC
The CAC score (Agatston score) was calculated by the computer automatically. The calcifications of coronary arteries were defined as a calcified plaque occupied more than 1 mm² with an attenuation =130 HU. The score of CAC in each target part was obtained by multiplying the sum of the size of the calcified plaques with the coefficient of CT peak values (130-199 Hu: 1; 200-299 Hu: 2, 300-399 Hu: 3, and >400 Hu: 4). The sum of the scores of CAC in all target parts was the total CAC score.

EBCT image processing
The raw image data were transferred to an Accuimage workstation (Accuimage Inc, USA) to render the three-dimensional reconstructions of coronary arteries. The cross-sectional images were screened for motion artifacts. The supplemental displaying techniques included maximum intensity projection (MIP), curved planar reformation (CPR), and volume reappearance (VR). The reconstructed 3-dimensional images were analyzed by 2 radiologists who were blinded to clinical diagnoses. The coronary tree was divided into segments according to the American Heart Association guidelines. Only segments of the left main stem, segments 1–3 of the right coronary artery, segments 5-8 of the left coronary artery, and segment 11 (circumflex artery) were analyzed for number of segments of stenosis of greater than 50%. All stenosis found on EBCTA was assigned to the same standardized diagram. Coronary segments distal to a vessel occlusion were not considered for analysis.

Coronary angiography
Coronary angiography was performed on 17 patients with diabetes who have coronary artery stenosis in EBCTA and all patients with CHD using the Judkins technique. Protocols were analyzed by two independent experienced cardiologists.

Statistical analysis
SAS 9.0 software package was used for statistical analysis. Data were expressed as percentiles and median (quartile) and mean±SD. The comparison between groups was performed using Chi square test, Kruskal-Wallis rank sum test, and analysis of variance (ANOVA). The Spearman correlation analysis of the indices was also performed. Multiple logistic regression analysis was used to calculate odds ratios and P values.
Results

Patient demographics
The distribution of age and sex is proportional among all the groups. Table 1.

Score of CAC and number of stenosed coronary artery segments (Table 2)
The score of CAC in 94 subjects ranged from 0 to 1120 (Table 2), with 0-33 in the normal control group, 0-379 in the diabetes group, 0-704 in the IGT group, and 0-1120 in the CHD group. Although a growing tendency of CAC score was demonstrated in the diabetes, IGT, and CHD groups, it did not reach a statistical significance from the control (\(P >0.05\)). More stenosed coronary artery segments were detected in diabetes (2.964±1.915), IGT (2.200±2.024), and CHD (2.273±1.679), as compared with control (0.520±1.295, \(P<0.05\)).

Correlation analysis of CAC and coronary artery tenosis
The correlations of age, fasting blood glucose, postprandial blood glucose, triglyceride, total cholesterol, HDL-C, and LDL-C to CAC score and number of segments of coronary artery stenosis were determined. Spearman’s rank correlation coefficient is calculated because CAC scores look like non-normally distributed data. Pearson’s product-moment correlation coefficient is calculated otherwise.

It was found that CAC score was related to patient age (\(r=0.423, P=0.001\)), but not to other indices. The number of stenosed coronary artery segments was associated with age (\(r=0.215, P=0.019\)), postprandial blood glucose (\(r=0.224, P=0.015\)), duration of diabetes (\(r=0.208, P=0.004\)), and total cholesterol (\(r=0.323, P=0.000\)). Table 3.

Risk analysis of CAD
Of the 94 participants in this study, those who showed both CAC and/or coronary artery stenosis were defined as patients with CAL. Potential CAD risk factors including age, sex, having/not having abnormal blood glucose, having/not having abnormal blood lipid (triglyceride>1.7mmol/L, total cholesterol>5.2mmol/L, HDL-C<1.0mmol/L), and having/not having CHD were used as independent variables in the logistic regression analysis. The incidences of CAL in diabetes (96.43%), IGT (93.33%), and CHD (90.91%) were substantially higher than that in normal control (56.00%, \(P<0.01\)). Table 2. It was noticed that CAL was associated with the presence of two factors, those being abnormal blood glucose (\(x^2=4.351, P=0.037\)) and CHD (\(x^2=12.116, P=0.0005\)). However, it was not correlated with other risk factors (\(P<0.05\)). The OR values of abnormal blood glucose and CHD were 7.514 (95% confidence interval: 1.885-63.778, \(P=0.05\)) and 12.876 (95% confidence interval: 1.565-105.945, \(P=0.018\)), respectively.

Contrast of EBCT, EBCTA and invasive coronary angiography (Fig 1)
EBCTA and coronary angiography were performed on a portion of patients with diabetes (n=17) and all patients with CHD (n=11). The result showed that there are many noncalcified plaques and stenoses in both groups of patients with diabetes and CHD. The rate of noncalcified plaques is 32%.

Discussion
It has been generally accepted that the occurrence of

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Table 1. Characteristics of the study sample(x±SD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control(n=25)</th>
<th>IGT(n=30)</th>
<th>Diabetes(n=28)</th>
<th>CHD(n=11)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50.9±9.1</td>
<td>46.4±6.1</td>
<td>52.1±7.1</td>
<td>54.9±14.5</td>
<td>0.203</td>
</tr>
<tr>
<td>Total cholesterol(mmol/L)</td>
<td>4.066±2.625</td>
<td>4.987±0.850</td>
<td>10.792±22.076</td>
<td>4.801±0.984</td>
<td>0.500</td>
</tr>
<tr>
<td>Triglyceride(mmol/L)</td>
<td>1.720±1.366</td>
<td>2.273±1.804</td>
<td>2.583±2.317</td>
<td>2.763±3.186</td>
<td>0.444</td>
</tr>
<tr>
<td>LDL-C(mmol/L)</td>
<td>2.595±0.724</td>
<td>2.566±0.824</td>
<td>2.856±1.065</td>
<td>2.689±0.795</td>
<td>0.777</td>
</tr>
<tr>
<td>HDL-C(mmol/L)</td>
<td>1.186±0.228</td>
<td>1.247±0.302</td>
<td>1.258±0.335</td>
<td>1.165±0.244</td>
<td>0.688</td>
</tr>
<tr>
<td>Fasting blood glucose(mmol/L)</td>
<td>4.476±0.554b</td>
<td>4.920±0.713b</td>
<td>8.088±3.395</td>
<td>4.900±0.505b</td>
<td>0.000</td>
</tr>
<tr>
<td>Postprandial blood glucose(mmol/L)</td>
<td>5.708±1.267**</td>
<td>8.530±0.906b</td>
<td>15.994±3.538</td>
<td>5.661±1.229**</td>
<td>0.000</td>
</tr>
</tbody>
</table>

* \(P<0.01\) vs diabetes group, *\(P<0.05\) vs IGT

Table 2. Incidence of CAD, score of CAC and segments of stenosed coronary arteries in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>Incidence of CAD (%)</th>
<th>Score of CAC/M (quarter range)</th>
<th>Number of stenosed coronary arteries segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>25</td>
<td>56.00</td>
<td>0.00 (0.00)</td>
<td>0.520±1.295</td>
</tr>
<tr>
<td>IGT</td>
<td>30</td>
<td>93.33&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.00 (34.00)</td>
<td>2.200±2.024&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28</td>
<td>6.43&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.00 (92.00)</td>
<td>2.964±1.915&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>CHD</td>
<td>11</td>
<td>90.91&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.00 (68.00)</td>
<td>2.273±1.679&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* \(P<0.01\) vs Normal control group.
Table 3. Correlations between demographic and biochemical variables, and log-transformed coronary calcium scores and number of stenosed coronary arteries segments in 94 cases.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coronary calcium scores</th>
<th>Number of stenosed coronary arteries segments</th>
<th>Correlation coefficient</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.423</td>
<td>0.000</td>
<td>0.215</td>
<td>0.019</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>0.044</td>
<td>0.638</td>
<td>0.208</td>
<td>0.004</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>0.077</td>
<td>0.413</td>
<td>0.094</td>
<td>0.314</td>
</tr>
<tr>
<td>Postprandial blood glucose (mmol/L)</td>
<td>0.030</td>
<td>0.746</td>
<td>0.224</td>
<td>0.015</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>0.143</td>
<td>0.125</td>
<td>0.323</td>
<td>0.000</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.045</td>
<td>0.629</td>
<td>0.165</td>
<td>0.074</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.167</td>
<td>0.073</td>
<td>-0.030</td>
<td>0.745</td>
</tr>
</tbody>
</table>

Fig. 1. EBCT plain scanner (A), EBCTA (B) with CPR, and invasive angiogram(C) of the right coronary artery (RCA) in a patient with diabetes. This demonstrates the multiple calcification (A). A no calcification plaque and high-grade stenosis are clearly seen in the mid-RCA of EBCTA (B, arrowhead). The corresponding are seen in the invasive angiogram.

EBCT plain scanner (D), EBCTA (E) with MIP and invasive angiogram (F) of left mainliner (LM), the left anterior descending artery (LAD) in a patient with CHD. Multiple calcification (D) is noted in the LM and LAD. Soft plaque and mid-high grade stenosis in the distal LM and proximal LAD are seen in the EBCTA (E, arrowhead).
cardiovascular events in patients with diabetes is much higher than those without it. The most recent guidelines of the National Cholesterol Education Program recommend that diabetes mellitus be considered a CAD equivalent, owing to the high incidence of atherosclerosis-related events in patients suffering from this disease. Raggi et al. followed 10,377 asymptomatic individuals (903 diabetic patients). They showed that the presence of any degree of coronary artery calcium in patients with diabetes mellitus portends a higher risk for all-cause mortality than in nondiabetic patients. Additionally, the absence of coronary artery calcium indicated a low short-term risk of death for diabetic patients as well as for subjects without diabetes. Therefore, early diagnosis of CAD, as well as early intervention, is vital for improving quality of life and reducing the disability ratio in patients with type 2 diabetes.

However, some studies indicate that the prevalence and severity of CAD in diabetes patients is not similar among ethnically diverse populations. The incidence of cardiovascular complications in Asians is generally lower than that of whites. However, the figure has increased substantially over the last two decades since more and more Asians are following the lifestyle of Western society such as higher caloric intake, relative excess of dietary saturated fats content and lack of fibers, together with reduced level of physical activities. In this study, we performed cardiac EBCT and EBCTA on patients with type 2 diabetes to find the prevalence of CAD in Chinese patients with type 2 diabetes mellitus. It was found that the occurrence of CAD in adults with abnormal level of blood glucose (IGT and diabetes) was more frequent than that in normal blood glucose subjects, whereas it was almost equal to that in patients with CHD. It was shown that the number of coronary artery stenosis segments was obviously higher as well in patients with an abnormal level of blood glucose as compared to those with normal blood glucose (P<0.01) and a growing tendency of CAC scores in patients with an abnormal level of blood glucose. The relative risk of CAL in diabetes was 7.514 (95% confidence interval: 1.885-63.778) with markedly statistical significance from non-diabetes. These results are similar to the previous studies on white people, suggesting the prevalence of CAD in Chinese type 2 diabetics and that blood glucose was an independent risk factor for CAD.

Although currently recognized risk factors for CAD are helpful in predicting the development of atherosclerosis, their ability to identify individual patients at risk of events is limited. The clinical application of coronary angiography and intracoronary ultrasound is useful to identify the coronary artery lesions in diabetic patients and currently remain the diagnostic standard for identification of CAD. However, there are issues due to their invasive nature and necessity of hospitalization. On the contrary, EBCT and EBCTA have been gradually accepted by physicians as a means to identify CAC and coronary artery stenosis, and recognized for their noninvasiveness, repeatability, and accuracy.

CAC is a novel marker of underlying atherosclerotic disease. CAC score is an important index for evaluating the severity of calcification displayed by EBCT. It was reported that the CAC score in CAD patients complicated by diabetes was higher than that in CAD patients without diabetes. Nevertheless, CAC score varies with age, sex, disease, and ethnicity, as described in previous studies, leading to different results from reports. Araneta et al. reported that Filipinos have no excess of CAC score despite their significantly higher prevalence of type 2 diabetes, metabolic syndrome, hypertension, and visceral adiposity than that of white women. In addition, no correlation was demonstrated between stenosis degree and calcification score among individual vessels in patients with positive calcium scan. CAC measured by EBCT is not an accurate marker for assessing the stenosis degree of coronary arteries in uremic patients.

In patients with acute coronary syndrome, noncalcified plaques were observed in as much as 36% of plaque-occupied segments. It was revealed that in patients with acute coronary syndrome, the mean ratio of segments with calcified plaques to segments with noncalcified plaques is close to 1:1. Our studies also provided clear evidence that there is no statistically significant difference of CAC scores existing between control and IGT, or diabetes and CHD (P=0.05). Multifactor correlation analysis demonstrated that CAC score was correlated with the patients' age, but not with blood glucose or blood lipid. EBCTA also revealed many noncalcified plaques and stenoses in both diabetes and CHD patients, which were demonstrated by coronary angiography. The rate of noncalcified plaques reached 32%. Based on these findings, we consider that CAC or CAC scoring alone cannot sufficiently reflect CAD, especially in the Chinese population. Because the sample size of this study is relatively small, this observation needs to be demonstrated in a larger size sample study.

EBCTA appears to be superior to calcium scoring in evaluating coronary anatomy, or in demonstrating both the coronary lumen and the soft plaques in the artery wall, especially while there are no significant flow-limiting stenoses by invasive angiography. It was reported that, using conventional angiography as the gold standard, the sensitivity and specificity of EBCTA for identifying the left anterior descending and the left main coronary artery stenoses were 92% and 94%, respectively. Another study verified that significant coronary artery stenosis could be correctly ruled out in 93% of segments with EBCTA. In our hospital, the accuracy rate of EBCTA for evaluation of normal coronary artery was 91.7% and 93.8%, and was 83.1% and 88.1% for evaluation of vessels with stenosis occupying more than 50% the diameter of the coronary artery. Vessel diameters in EBCTA and coronary angiography correlated reasonably well, and the correlation coefficient reached 0.78, indicating the appearances by EBCTA are highly indicative of coro-
Coronary artery lesions. Our studies also provided clear evidence that the number of stenosed arteries segments in patients with diabetes is more than that in the control. Multifactor correlation analysis demonstrated that the stenosed artery number was tightly associated with age, postprandial blood glucose, and cholesterol. We consider that CAC alone should not be used as a standard screening test for atherosclerotic coronary disease evaluation in Chinese type 2 diabetic patients. Three-dimensional reconstructed images of the coronary artery by EBCT and EBCTA could better track the progression of coronary artery lesions in diabetes patients.

Acknowledgments

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