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Combined arteriosclerotic assessment of ankle-brachial index and maximum intima-media thickness via CCTA is useful for predicting coronary artery stenosis in patients with type 2 diabetes

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ABSTRACT

Aims: Patients with diabetes mellitus (DM) are likely to develop asymptomatic myocardial infarction as a complication. However, coronary artery lesions are difficult to assess in internal medicine. This study aimed to develop a prediction formula for coronary artery stenosis, as determined by coronary computed tomographic angiography (CCTA), by analyzing risk factors in patients with type 2 DM.

Methods: A prediction formula was developed based on a multivariate analysis of common factors in patients with ⩾50% coronary artery stenosis in a cohort of 327 patients with type 2 DM who underwent CCTA between 2007 and 2009, and cutoff values were calculated (derivation study). The validity of the optimal cutoff value was confirmed in a separate cohort of 317 patients with type 2 DM who underwent CCTA between 2010 and 2011 (validation study).

Results: In the derivation study, five predictive factors (presence/absence of hypertension, estimated glomerular filtration rate, maximum intima-media thickness [max-IMT], ankle-brachial index [ABI], and use/nonuse of diabetic medication) were used to develop a prediction formula. In the validation study, positive predictive value (PPV) and negative predictive value (NPV) of the cutoff value derived from the prediction formula were 53% and 73%, respectively.

Conclusions: We developed a novel formula to predict coronary artery stenosis using five predictive factors. This formula is useful for determining whether computed tomography (CT) examination is necessary, even in clinical settings without CCTA equipment. Early detection of coronary artery stenosis in patients with DM may also lead to better health outcomes.

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1. Introduction

The incidence of type 2 diabetes mellitus (DM) is increasing worldwide [1]. Approximately one-third of all patients with type 2 DM live in Western Pacific countries, including Japan. The prevalence of type 2 DM in this region was reported to be 8.6% in 2013, and the number of patients with diabetic complications is increasing. Therefore, appropriate treatment of the disease and prevention of its complications are vital. Diabetic complications are largely divided into microvascular and macrovascular complications. Studies such as the Kumamoto Study [2] and the United Kingdom Prospective Diabetes Study 33 (UKPDS 33) [3] demonstrated that intensive glycemic control prevents microvascular complications. However, another study reported that silent myocardial ischemia occurred in 22–39% of patients with type 2 DM who already had an autonomic disorder as a complication [4].

Currently classical risk factors for ischemic heart disease, which is a major macro vascular complication of type 2 DM, include smoking, dyslipidemia, hypertension, type 2 DM, family history of heart disease, age, and sex [5–8]. Myocardial infarction is the most serious macrovascular complication of type 2 DM. Type 2 DM was shown to be a risk factor for developing myocardial infarction in the Framingham Study [9] and the UKPDS 35 [10]. However, the classical risk factors alone do not sufficiently predict the occurrence of coronary artery disease [11,12]; therefore, direct evaluation of the condition of the coronary artery is important in type 2 DM patients.

Multi-detector computed tomography (MDCT) is an important instrument for detecting coronary artery stenosis. Recent advances in MDCT allow non-invasive and rapid evaluation of the coronary artery. With the development of this technology, the accuracy of diagnosing coronary artery stenosis has improved. A study investigating the accuracy of 64-slice MDCT in assessing coronary artery stenosis reported that the overall sensitivity, specificity, positive predictive value, and negative predictive value for classifying stenosis were 94%, 97%, 87%, and 99%, respectively [13]. Coronary computed tomography angiography (CCTA) is a specialized method for evaluating the coronary artery in MDCT. However, CCTA is not recommended for the screening of coronary artery disease in every patient with type 2 DM because it requires radiation exposure and contrast agents.

The purpose of this study was to develop a model for predicting significant coronary artery stenosis in patients with type 2 DM by examining the association between coronary artery stenosis as assessed by CCTA and background risk factors. The cohort was divided into two groups; one cohort was used for a derivation study and the second cohort was used for a validation study. A prediction model was developed using the data from the first cohort, and the validation was performed using the data from the second cohort. In addition, we compared the ability of the developed model to predict coronary artery stenosis using subject data applied to the UKPDS risk engine score, which estimated 10-year non-fatal coronary heart disease risk.

2. Material and methods

2.1. Subjects

All subjects were Japanese patients with type 2 DM who underwent CCTA at Jinnouchi Hospital from June 2007 to September 2011. We considered subjects eligible when they fulfilled the following criteria: age 40 years or older at the time of enrollment and diagnosis of type 2 DM by diabetologists based on the Japan Diabetes Society's criteria [14]. Based on these initial eligibility criteria, study subjects needed to meet at least one of these additional metrics for CCTA: (1) type 2 DM duration of $\geqslant$10 years, (2) HbA1c of at least $\geqslant$7%, (3) body mass index (BMI) of $\geqslant$25 kg/m^2, and/or (4) history of smoking and of having dyslipidemia. Study subjects underwent CCTA regardless of symptoms or signs. We omitted patients from the study with missing data prior to study entry. Patients were divided into derivation and validation cohorts (Fig. 1). The derivation cohort comprised 327 patients who underwent CCTA from June 2007 to December 2009, and the validation cohort comprised 317 patients who underwent CCTA from January 2010 to September 2011. Significant coronary artery stenosis was defined as the presence of at least one stenotic lesion with $\geqslant$50% coronary artery obstruction. The exclusion criteria were (1) renal insufficiency, (2) contrast allergy, (3) revascularization, (4) asthma, and (5) cardiac arrhythmias. Patients with severe coronary calcification were excluded due to the associated difficulty in evaluating the coronary lumen. Severe coronary calcification was defined as the lumen not being able to be described by short-axis view. The study protocol was approved by Jinnouchi Hospital's committees on the ethics of human research. All subjects enrolled in this study provided written informed consent.

2.2. Assessment of coronary artery disease by CCTA

CCTA was performed with a 64-slice MDCT scanner (LightSpeed VCT, GE Medical Systems, Waukesha, Wisconsin, USA) with 64 $\times$ 0.625-mm section collimation, a 350 or 400-ms rotation time, a 120-kV tube voltage, and a pitch from 0.16 to 0.18 depending on the patient's heart rate. The estimated mean radiation dose was 15–18 mSv. A non-contrast scan was initially performed to determine anatomical landmarks for the contrast-enhanced study. Immediately thereafter, test bolus tracking with 10 mL of a non-ionic contrast agent was applied to calculate the exact arrival time of the contrast agent in the coronary arteries, with a region of interest in the proximal part of the ascending aorta. Finally, a contrast-enhanced scan with retrospective electrocardiogram gating was performed after administration of the contrast medium (220 mg I/kg body weight/10 s) during a single breath hold. Image reconstruction was performed using image analysis software (CardIQ, GE Healthcare) on a dedicated computer workstation (Advantage Workstation Ver. 4.2, GE Healthcare). A standard kernel was used as the reconstruction filter. Depending on the patient's heart rate, either a half-scan or multi-segment reconstruction algorithm was selected or the optimal cardiac phase with the fewest motion