ORIGINAL ARTICLE
DOI: 10.3904/kjim.2009.24.3.183

Early Detection of Asymptomatic Coronary Artery Disease in Patients with Type 2 Diabetes Mellitus

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Background/Aims: In type 2 diabetic patients, coronary artery disease (CAD) is usually detected at an advanced stage due to a lack of symptoms. The aim of this study was to define which clinical parameters or non-invasive tests predict CAD in asymptomatic type 2 diabetic patients.
Methods: One hundred fourteen asymptomatic type 2 diabetic patients were divided into two groups based on the number of cardiovascular disease (CVD) risk factors (group A ≥2, group B ≤1). Treadmill exercise ECG tests (TMT) were conducted in all cases, and coronary artery angiography was performed on TMT-positive patients. Clinical parameters, diabetic status, and coronary angiographic findings were analyzed.
Results: The prevalence of CAD was 41.0% in group A and 16.7% in group B. The number of risk factors was significantly correlated with the prevalence of CAD, but not with the severity of CAD. Multivariate analysis showed that family history of CAD (odds ratio [OR]=9.41; 95% confidence interval [CI], 1.60-55.49) and diabetes duration ≥10 years (OR=3.28; 95% CI, 1.29-8.84) were independent CAD risk factors in asymptomatic patients.
Conclusions: We recommend a routine screening for CAD in type 2 diabetic patients who have a longer (≥10 years) diabetic duration or a family history of CAD, even if they are asymptomatic for CAD. **(Korean J Intern Med 2009;24:183-189)**

Keywords: Diabetes mellitus, type 2; Coronary artery disease; Early diagnosis; Risk factors

INTRODUCTION

Coronary artery disease (CAD) accounts for 70-80% of mortalities in diabetic patients, and type 2 diabetes mellitus (DM) is an important risk factor [1]. CAD risk for those with type 2 DM is as great as that associated with a previous history of myocardial infarction [1-3]. However, progressive CAD is asymptomatic in many cases of type 2 DM, which makes it difficult to diagnose at the proper time [4]. The diagnosis of asymptomatic CAD in type 2 diabetic patients is largely made based on the recommendations of the American Diabetes Association (ADA). The ADA recommends that DM patients perform a treadmill exercise test (TMT) or a coronary artery angiography if they have additional cardiovascular disease (CVD) risk factors [5]. However, clinically severe CAD is often discovered in patients with fewer risk factors.

To overcome these limitations, several previous studies were conducted to develop more sensitive diagnostic methods, such as single photon emission computerized tomography (SPECT) [6] and multi-detector coronary CT [7]. However, more sensitive diagnostic approaches may be unrealistic because clinicians care for asymptomatic diabetic patients on an outpatient basis. Thus, no proper diagnostic test exists for the early diagnosis of asymptomatic CAD. In the present study, TMT and

Received: November 5, 2008
Accepted: March 16, 2009

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coronary arterial angiography (CAG) were performed in asymptomatic type 2 diabetic patients, regardless of the number of CVD risk factors present, to determine the best CAD predictor in these patients.

METHODS

Subjects

This study was performed prospectively from 2000 to 2006. One hundred fourteen type 2 DM patients were enrolled based on a detailed history obtained from all type 2 DM patients who visited the department of endocrinology, Dankook University Hospital. Patients were excluded if they 1) had clinical symptoms of typical angina or chest pain, or had undergone tests for CVD (TMT, exercise echocardiography, myocardial SPECT, and CAG); 2) had abnormal ECG findings during CVD tests such as TMT, myocardial SPECT, and CAG; and 3) were previously diagnosed or treated for non-CAD heart diseases such as an inherited cardiac disorder, cardiac valve disease, heart failure, or arrhythmia. We also excluded cases with ambiguous information related to CVD.

TMT was performed in all patients regardless of the numbers of CVD risk factors. Coronary arterial angiography was conducted in patients with positive or equivocal TMT results, for example, test discontinuation due to a decline in exercise ability. Results were taken from the first test if patients underwent tests more than once. This study was approved by the Hospital Ethics Committee, and informed consent for coronary angiography was obtained from all patients.

Evaluation of clinical factors

Age, gender, height, and body weight were measured. The body mass index (BMI) was calculated at the time of testing. Obesity was defined as a BMI ≥25. A family history of type 2 DM was defined as a diagnosis of DM among first degree relatives. A family history of CAD was defined as a diagnosis of myocardial infarction or angina pectoris among first relatives. Those with a smoking history were defined as smokers regardless of current smoking status or amount of smoking. Hypertension was defined as taking anti-hypertensive medication, a systolic pressure ≥140 mmHg, or a diastolic pressure ≥90 mmHg on two separate occasions, as defined by the World Health Organization. The five CVD risk factors were smoking, hypertension, dyslipidemia, a family history of CAD, and macro-micro albuminuria, based on the 1998 ADA recommendations [5]. According to the number of risk factors, 114 patients were divided into two groups: Group A with ≥2 risk factors, and Group B with ≤1.

Type 2 DM patients were defined as: 1) diagnosed and received treatment for DM, 2) random blood glucose level ≥200 mg/dl with diabetic symptoms based on the ADA diagnostic criteria, or 3) fasting blood glucose level of ≥126 mg/dl. Duration of type 2 DM was defined as the time lapse from diagnosis to the time of CAD testing and was measured in years. Diabetic retinopathy was defined as 1) a diagnosis by fundoscopic examination (by a professional ophthalmologist) and 2) a history of photocoagulation treatment due to diabetic retinopathy. Diabetic neuropathy was defined as the presence of neuropathic symptoms (paresthesia, pain), signs of sensory loss (loss of light touch, pinprick, cold, vibration in the toes), abnormal findings on the Semmes-Weinstein monofilament test, and nerve conduction velocity measurements. Diabetic nephropathy was defined as the appearance of abnormal urinary albumin levels; microalbuminuria (30-299 mg albumin/24 hours) and macroalbuminuria (>300 mg albumin/24 hours).

Biochemistry tests

Fasting plasma glycosylated hemoglobin (HbA1c), total cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol were measured. The Friedewald equation (LDL-cholesterol=total cholesterol-HDL cholesterol - triglyceride/5) was used to calculate low-density lipoprotein (LDL)-cholesterol if triglyceride was <400. LDL-cholesterol was directly measured if triglyceride was ≥400. According to the ADA guideline [5], dyslipidemia was defined as a total cholesterol level ≥240 mg/dL, an HDL-cholesterol level of 35 mg/dL or less, or an LDL-cholesterol level ≥160 mg/dL.

Treadmill exercise ECG test

TMT was performed according to the Bruce protocol using a 12-lead ECG. TMT was terminated if the heart rate (220-age) reached 85% of target, the patient complained of significant chest pain, systolic blood pressure dropped by 10 mmHg or more during the test, the patient developed a neurologic impairment such as dizziness or vertigo, the patient had blood flow impairment such as cyanosis, the patient had continuous ventricular arrhythmia, or the ST segment declined or became elevated more than 1.0-1.5 mm [8]. A positive

finding on the TMT was defined as more than a 1-mm horizontal down-sloping or up-sloping ST-segment depression that occurred at least 0.08 seconds after the J point. Findings were considered "uncertain" in cases with a positive treadmill exercise test and an inappropriate outcome, such as reduced exercise capacity or disruptions in heart rate. Coronary arterial angiography was conducted in the cases showing positive or uncertain findings during TMT.

Coronary arterial angiography

The femoral artery (usually the right) was catheterized using the Seldinger technique. The femoral approach was preferred because all of the patients in this study showed positive findings on the TMT, and they had a high probability of percutaneous coronary intervention. Two or more Judkins coronary catheters were used for diagnostic coronary angiography, and proper interventional instruments were used if coronary intervention was necessary. Angiographic data were obtained using a fully digital Annova 2100 (GE Health Care, Waukesha, WI, USA) and analyzed using a QCA algorithm (GE stenosis analysis algorithm, GE Health Care). CAD was considered in case of more than 50% stenosis. In cases with stenosis >80% (severe case), a Percutaneous coronary intervention (PCI) including balloon angioplasty and stent insertion was performed with or without the aid of intravascular ultrasound. All patients who underwent PCI were closely observed in a sub-intensive care unit.

Statistical analysis

SPSS (version 11.5 for Windows) was used for the statistical analysis. When a parameter showed a skewed distribution, median values between the two groups were compared with the nonparametric Mann-Whitney *U*-test. Mean±standard deviations (SD) were compared using an unpaired Student's *t*-test for normally distributed parameters. The CAD incidence based on the number of risk factors was analyzed using the chi-square test. Logistical regression analysis was used to identify CAD risk factors in asymptomatic patients. P values <0.05 were considered significant.

RESULTS

Patient characteristics

The clinical characteristics of all asymptomatic patients

Table 1. Clinical characteristics, diabetic complications, and risk factors for cardiovascular disease in the subjects

	Total	CAD		
	(n=114)	Yes (n=38)	No (n=76)	*p* value
Age, years	57.2±10.7	60.5±8.0	55.5±11.5	<0.05
Male/female	65 / 49	18 / 20	47 / 29	NS
BMI, kg/m^2	25.1±3.4	24.9±2.7	25.2±3.7	NS
DM duration, years	10.2±7.6	13.4±7.0	8.4±7.5	<0.001
DM family history	45 (39.5)	17 (44.7)	28 (36.8)	NS
Retinopathy	43 (37.7)	18 (47.3)	25 (32.8)	NS
Neuropathy	43 (37.7)	18 (47.3)	25 (32.8)	NS
Hypertension	60 (52.6)	27 (71.1)	33 (43.4)	<0.05
Smoking	55 (48.2)	16 (42.1)	39 (51.3)	NS
CAD family history	9 (7.9)	7 (18.4)	2 (2.6)	<0.001
Proteinuria	36 (31.6)	16 (42.1)	20 (26.3)	NS
Risk factors	2.0±1.0	2.5±0.9	1.8±0.9	<0.001
HbA1c, %	9.0± 2.0	8.6±1.7	9.1±2.2	NS
Creatinine, mg/dL	1.1±0.6	1.2±0.9	1.0±0.3	NS
Total cholesterol, mg/dL	198.3± 41.4	207.5±39.1	193.7±42.0	NS
HDL cholesterol, mg/dL	45.0±11.3	48.0±11.3	43.6±11.0	NS
LDL cholesterol, mg/dL	116.1± 36.0	123.2±38.0	112.4±37.6	NS
Triglyceride, mg/dL	216.7±140.0	204.9±134.9	224.4±124.5	NS

Values are number (percentage) or mean±SD.
P values refer to comparisons between patients with and without CAD based on coronary angiographic findings.
CAD, coronary artery disease; BMI, body mass index; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Odds ratios for coronary artery disease risk factors

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age >59 years	2.68 (1.18-6.08)	2.56 (0.95-6.88)
Hypertension	3.20 (1.39-7.37)	1.94 (0.72-5.21)
CAD family history	8.36 (1.64-42.49)	9.41 (1.60-55.49)*
DM duration ≥10 years	3.78 (1.58-9.05)	3.38 (1.29-8.84)*
Risk factors ≥2	3.48 (1.30-9.32)	2.08 (0.68-9.41)

OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; DM, diabetes mellitus.
* $p<0.05$.

(male, n=65; female, n=49) are shown in Table 1. The mean BMI was 25.1, and approximately half of the patients were overweight. The mean duration of DM was 10.2 years. Dyslipidemia was the most prevalent CVD risk factor. The average number of CVD risk factors was 2.0 (Table 1).

To identify CAD-related risk factors, we compared clinical CVD risk factors between patients with CVD and patients without CVD (Table 1). Those with CAD were older and they had a longer duration of DM, hypertension, a more frequent family history of CAD, and a larger number of CVD risk factors. No significant differences were found in gender, obesity, complications from chronic DM, smoking status, HbA1c, creatinine, total cholesterol, HDL-cholesterol, LDL-cholesterol, or triglyceride values (Table 1). The odds ratios for the risk factors were (in order); a family history of CAD, type 2 DM duration of ≥10 years, ≥2 risk factors, hypertension, and age ≥59 years (Table 2). In the multivariate analysis, only a family history of CAD and DM duration ≥ 10 years were significantly correlated with the presence of CAD in asymptomatic patients (Table 2).

Risk factor analysis

The 114 subjects were classified by the number of CAD risk factors, as suggested by the ADA [5]. Seventy-eight patients (68.4%) had two or more risk factors (group A), and 36 patients (31.6%) had one or fewer risk factors (group B). No significant differences in age, BMI, complication status, blood glucose level, family history, or DM duration were found between groups A and B (Table 3). The CAD prevalence in groups A and B was 41.0% and 16.7%, respectively ($p<0.01$). These data confirm that the number of risk factors was correlated with CAD incidence. However, when we compared the two groups by CVD severity, group A had 21 (65.6%) severe cases (≥80% stenosis) and group B had four (66.7%). Thus, CVD severity was not different between the two groups, suggesting that even asymptomatic patients with few risk factors could have severe CAD.

Analysis of patients with one or no risk factors

According to the ADA recommendations, diagnostic evaluation of patients in group B with one or fewer risk factors would not be required. If we followed the ADA recommendation, we would have missed six CVD patients who had confirmed CAD by coronary artery angiography. Thus, we further analyzed the clinical characteristics of these six patients in detail (Table 4). Their mean age was 64.5 years, and the mean DM duration was 16.2 years. Furthermore, five had diabetic retinopathy, and four had

Table 3. Comparison between patients who had greater than two (group A) or one or fewer (group B) cardiovascular disease risk factors

	Group A (n=78)	Group B (n=36)	*p* value
Age, years	57.6±9.9	56.2±12.3	NS
Male/female	46/32	19/17	NS
BMI, kg/m^2	25.2±2.8	24.8±4.4	NS
DM family history	29 (37.2)	16 (44.4)	NS
DM duration, years	10.3±7.5	9.6±8.0	NS
Retinopathy	33 (42.3)	10 (27.8)	NS
Neuropathy	30 (38.5)	13 (36.1)	NS
HbA1c, %	9.1±2.1	8.7±2.0	NS
Incidence of CAD	32 (41.0)	6 (16.7)	0.010
Severe CAD cases*	21 (65.6)	4 (66.7)	NS

Values are number (percentage) or mean±SD.
NS, not significant; BMI, body mass index; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; CAD, coronary artery disease.
* Severe CAD cases refers to the number (%) of patients who underwent a reperfusion procedure due to 80% or greater stenosis.

Table 4. Clinical characteristics of the six patients in group B

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	F	F	F	M	F	M
Age, years	65	65	71	71	66	49
BMI, kg/m^2	27.4	21.7	24.0	23.5	24.2	18.6
DM duration, years	20	20	15	10	30	2
Risk factor	HTN	HTN	DysL	Smoking	DysL	Smoking
HbA1c, %	9.8	9.2	9.0	7.5	10.9	11
DM treatment	Insulin	Insulin	OHA	OHA	Insulin	Insulin
Retinopathy	+	+	+	+	+	-
Neuropathy	+	+	+	-	-	-
Nephropathy	-	-	-	-	-	-
Echocardiography	Normal	Normal	Normal	Normal	Normal	Normal
CAG findings	Multi	Single	Multi	Multi	Multi	Multi
Reperfusion	+	-	-	-	+	+

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; DysL, Dyslipidemia; HbA1c, glycosylated hemoglobin; OHA, oral hypoglycemic agent; CAG, coronary arteriography; Multi, multi-vessel disease; Single, single vessel disease.

diabetic neuropathy. Four were treated with insulin, and the other two patients were taking oral hypoglycemic drugs. Blood glucose control was poor in all six (mean HbA1c, 9.6%); however, none of the patients had abnormal echocardiographic findings. Three had a positive TMT result, and three an inappropriate TMT result, which was due to the patient's request to discontinue treadmill exercise because of poor exercise capacity. Coronary arterial angiography showed significant stenosis (≥80%) in four patients who required reperfusion therapy. Five of the six patients had multiple CAD, and two of the five had stenosis in three vessels (Table 4). In summary, except for one relatively young male with a 30-year smoking history (patient 6), the remaining five were elderly with a long duration of DM, poor glucose control, and various diabetic microvascular complications.

DISCUSSION

We found that the diagnostic approach that considers the number of CVD risk factors may fail to detect CVD in a substantial number of patients. Cost-benefit considerations probably make it impossible to adopt an active diagnostic approach in all asymptomatic patients. However, based on our results, we recommend an active CAD evaluation in older patients with a disease duration of ≥10 years and a family history of CAD.

CAD may have already progressed in DM patients at the time of diagnosis [9,10] or may present as heart or multiple organ failure, which have high mortality rates [11,12]. Nevertheless, a CAD diagnosis is often delayed, especially in asymptomatic cases. The prevalence of asymptomatic CAD in DM patients is diverse and reportedly ranges from 9 to 75% [13-17]. In the present study, the prevalence of CAD was 29.8% among asymptomatic patients and 16.7% among patients with one or no risk factors. These figures are somewhat lower than are those reported previously, partly because of the strict selection of asymptomatic patients; we tried to exclude all patients with any CAD-related symptoms based on a careful review by physicians.

Diabetes itself is one of the Framingham risk factors for ischemic heart disease. We used the ADA recommendation to search for risk factors because the guideline for "asymptomatic" diabetic patients is more specific and widely used in practice. The diagnostic approach based on the numbers of CVD risk factors in asymptomatic patients was devised in 1998 by the American Heart Association and at a Consensus Development Conference of the American Diabetic Association [5]. This approach is based on an epidemiologic study in which patients who had more than one of the following five CVD risk factors were more likely to have CAD: smoking, dyslipidemia, hypertension, family history of CAD, and macro-micro albuminuria. The relationship between the number of CVD risk factors and incidence is also clear in our study; a distinct difference was found between the group with two or more and that with one or fewer risk factors. However, when we compared CAD severity using the

number of patients who had undergone reperfusion therapy due to significant occlusions, no significant difference was observed between those who underwent reperfusion therapy and those who did not (65.5 vs. 66.7%). That is, CAD incidence in patients with a lower number of risk factors is relatively small, but disease severity is not negligible, which is why we must make efforts to identify CAD early.

We focused on the six asymptomatic patients with one or no CVD risk factors because these patients would previously have been considered to be a low risk group and warrant only clinically observation. Most of these patients (Table 4, case 1~5) were >60 years old, and the DM duration was more than 10 years. These five patients were not able to pass the second stage of the TMT, so a decline in TMT exercise capacity may be an important sign. The remaining patient (Table 4, case 6) was a relatively young man with no evidence of microvascular complications. This patient had distin-guished clinical features compared to the other five, and the main factor in this case might be atherogenic or vascular in nature rather than DM. We suggest that the clinical characteristics of these six patients could be used as reference data, even though they do not constitute a general parameter for a diagnostic approach due to the small number of patients.

The duration of DM is not included among CAD risk factors in the ADA recommendations. However, debate on the relationship between duration and CAD continues, and several recent reports have concluded that a positive correlation exists [13, 16-18]. Our study confirmed that it is advisable to consider the DM duration as a primary CAD risk factor, regardless of symptoms. Other risk factors, such as dyslipidemia, smoking [19], and macro-micro albuminuria [13,20] are well-known CVD risk factors, although we found no significant correlations in asymptomatic patients. It is unclear whether this discrepancy is specific to asymptomatic patients or is due to the selection process. We recruited subjects from an outpatient clinical setting, and not from among patients who had undergone coronary angiography or who had CAD symptoms. Hence, we believe that our patients mainly consisted of truly asymptomatic patients in a typical clinical setting.

Several attempts have been made to overcome the delayed detection of CAD using more sensitive diagnostic techniques. In a recent large-scale study [7], more significant coronary stenosis, multivessel involvement, and greater plaque burden were observed in subjects with impaired fasting glucose or diabetes by MDCT, even though they were asymptomatic. Without question, recent tools are more promising to detect asymptomatic patients earlier with higher accuracy. The problem is applicability. Although these sensitive diagnostic tools have important roles, they apply only to referral hospitals. Accordingly, TMT appears to be the most effective method for CAD screening in an outpatient clinical setting. In fact, it is the most efficient means to screen for asymptomatic CAD [13,15]. Our study results are limited due to the small number of subjects; thus, a large-scale future study using improved diagnostic techniques is warranted.

In summary, type 2 DM patients had a greater risk for CVD if they were old, had a longer DM duration, or had a family history of CVD, even if they were asymptomatic. We recommend that diagnostic tests be performed to detect CVD in these asymptomatic patients.

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