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Silent myocardial ischemia in asymptomatic patients with type 2 diabetes mellitus without previous histories of cardiovascular disease

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ABSTRACT

Background: The number of patients with type 2 diabetes mellitus (T2DM) continues to increase all over the world. Cardiovascular disease (CVD), especially coronary artery disease (CAD), is a major cause of the morbidity and mortality in patients with T2DM. The prognosis of patients with silent myocardial ischemia (SMI) is worse than that in those without.

Methods and results: Thus, to assess how many patients with SMI existed among those patients, CVD screening tests were performed in 128 asymptomatic patients with T2DM without previous histories of CVD. SMI could be detected in 24 patients (19%) by exercise stress tests and/or the coronary fractional flow reserve. Their 12-lead electrocardiogram and cardiac ultrasonography were both normal. Compared to those without SMI, those with had a statistically significant longer history of T2DM (17 ± 1 versus 11 ± 1 years, $p = 0.006$), and the co-existence of a family history of CVD (42% versus 21%, $p = 0.037$). Furthermore, these factors were demonstrated as independent risk factors of SMI by a multivariate analysis (Odds ratio 1.060 and 4.000, respectively), and in accordance with the disease duration of T2DM, the prevalence of patients with SMI has been increasing ($p = 0.019$).

Conclusions: Physicians should be aware of these conditions when examining patients with T2DM, especially with a family history of CVD and/or long disease duration (>11 years) of T2DM, even though they have no symptoms, previous histories of CVDs, and/or abnormal findings on the 12-lead electrocardiogram and cardiac ultrasonography. This may be an effective, safe, and attractive diagnostic strategy for those asymptomatic patients with T2DM.

1. Introduction

The number of patients with type 2 diabetes mellitus (T2DM) continues to increase all over the world, and will be likely to reach about 6 hundred million in 2035 [1]. There is evidence that the 10-year cardiovascular disease (CVD) risk among U.S. patients with T2DM has improved significantly over the past decade [2,3]. However, CVD, especially coronary artery disease (CAD), is still the leading cause of complications and death in those patients [4–6]. Recently, the Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013 [7] recommends screening tests for CVD, and it is desirable that those examinations should be performed in patients with T2DM once a year [7]. The aim of this study was to assess how many patients with CVD, especially CAD, exist among those asymptomatic patients with T2DM without previous histories of CVD.

2. Methods

2.1. Study population and laboratory analysis

This study was approved by the institutional review committee and ethics review board of our hospital. From 2014 to 2015, 128 asymptomatic out-patients (80 males and 48 females with a mean age of 69 ± 1 years and body mass index (BMI) of 24 ± 1) with T2DM and no previous history of CVD, including cerebral infarctions, carotid artery stenosis (CAS), CAD, renal artery stenosis, arteriosclerosis obliterans (ASO), and aortic aneurysms (AAs), underwent screening of CVD after informed consent was obtained at our hospital. All patients had their history recorded including the disease duration of T2DM, and underwent a physical examination, laboratory analysis, chest radiogram, 12-lead

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electrocardiogram, carotid, cardiac, and abdominal ultrasonography (Xario 200, TOSHIBA, Tokyo, Japan, and HI VISION Preirus, HITACHI, Tokyo, Japan), ankle brachial index, and coronary computed tomography [8] (CCT) (Aquilion 64, TOSHIBA, Tokyo, Japan). The disease duration of T2DM was defined as the duration from the time of being first diagnosed with T2DM by a laboratory analysis including a blood sugar test, HbA1c, and/or oral glucose tolerance test, up to present. The prevalence of major coronary risk factors included hypertension, dyslipidemia, ex- or current smoking, a family history of CVD, and the BMI and values of the HbA1c, LDL-cholesterol, HDL-cholesterol, LDL-cholesterol to HDL-cholesterol (LDL/HDL) ratio, triglycerides, eicosapentaenoic acid to arachidonic acid (EPA/AA) ratio, serum creatinine, and brain natriuretic peptide (BNP) were also measured. Although the Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013 [7] does not recommend routine CCT for screening for CAD in asymptomatic patients with T2DM, a recent clinical trial demonstrated that CCT can clarify the diagnosis, enable targeting of interventions, and reduce the future risk of myocardial infarctions [8]. Thus, we included CCT into the screening tests for CAD.

2.2. Evaluation of the internal drug use for DM and CVD

The prevalence of optimal medical therapies (OMTs) for the prevention of diabetes including insulin, sulfonylurea, metformin, α-glucosidase inhibitors (α-GI), thiazolidine-dione, rapid insulin secretagogue, dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP) -1 receptor agonists, sodium-glucose cotransporter (SGLT) -2 inhibitors, and diet alone, and of atherosclerosis including statins, anti-platelets, and renin–angiotensin system (RAS) inhibitors, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), were also evaluated.

2.3. Evaluation of myocardial ischemia

To evaluate the myocardial ischemia, the patients with severe coronary stenosis (stenosis > 50% of the left main trunk and > 75% of that except the left main trunk) and/or severe coronary calcifications detected by CCT underwent exercise stress testing and coronary angiography (CAG) with/without a fractionated flow reserve (FFR) measurement, as previously described [9]. All stenoses with an FFR of 0.80 or less and/or positive exercise stress testing were treated with medications and/or revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafts (CABG).

2.4. Statistical analysis

The numerical results are expressed in the text as the mean ± standard deviation. Paired data were compared by Student *t* tests. A multivariate logistic regression analysis was carried out to evaluate the association between the ischemia and a male sex, the age, disease duration of T2DM, hypertension, dyslipidemia, ex- or current smoking, family history of CVD, and the BMI. The trend in the proportions and correlation between the prevalence of SMI and the disease duration of T2DM was determined by a Cochran–Armitage analysis. All analyses were performed with SAS version 9.2 software (SAS Institute, Cary, NC). A $p < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Patient characteristics and laboratory analysis (Table 1)

Screening tests for CVD were performed in 128 out of 133 asymptomatic out-patients with T2DM without histories of CVD. Because 5 patients did not agree to undergo screening tests, they were excluded from the statistical analysis. No patients suffered from any screening- and/or procedure-related complications. In all patients, the average of the disease duration of T2DM, and the systolic and diastolic pressures were 13 ± 1 years, 128 ± 1 mm Hg, and 72 ± 1 mm Hg, respectively. The prevalence of the co-existence of hypertension, dyslipidemia, ex- or current smoking, and a family history of CVD was 75 (59%), 81 (63%), 60 (47%), and 32 (25%) patients, respectively. The values of the HbA1c, LDL-cholesterol, HDL-cholesterol, LDL/HDL ratio, triglycerides, EPA/AA ratio, serum creatinine, and BNP were 7.0 ± 0.1%, 105 ± 2 mg/dl, 58 ± 1 mg/dl, 1.96 ± 0.06, 135 ± 6 mg/dl, 0.42 ± 0.03, 0.78 ± 0.02 mg/dl, and 27 ± 3 pg/dl, respectively.

Table 1
Patient Characteristics.

	All (n = 128)	N-IS (n = 104)	IS (n = 24)	p value (N-IS vs. IS)
Male	80 (63%)	64 (62%)	16 (67%)	0.643
Age (years)	69 ± 1	68 ± 1	71 ± 2	0.311
Body mass index (kg/m^2)	24 ± 1	24 ± 1	23 ± 1	0.070
Duration of DM (years)	13 ± 1	11 ± 1	17 ± 1	0.006
Systolic BP (mm Hg)	128 ± 1	128 ± 1	130 ± 2	0.316
Diastolic BP (mm Hg)	72 ± 1	72 ± 1	69 ± 1	0.163
Co-existence				
Hypertension	75 (59%)	58 (56%)	17 (71%)	0.180
Dyslipidemia	81 (63%)	66 (63%)	14 (58%)	0.643
Smoking	60 (47%)	46 (44%)	14 (58%)	0.215
Family history of CVD	32 (25%)	22 (21%)	10 (42%)	0.037
Laboratory analysis				
HbA1c (%)	7.0 ± 0.1	7.0 ± 0.1	7.1 ± 0.1	0.665
LDL-cholesterol (mg/dl)	105 ± 2	105 ± 2	104 ± 5	0.739
HDL-cholesterol (mg/dl)	58 ± 1	58 ± 1	56 ± 3	0.630
LDL/HDL ratio	1.94 ± 0.06	1.95 ± 0.07	1.93 ± 0.12	0.898
Triglyceride (mg/dl)	135 ± 6	136 ± 7	134 ± 13	0.919
EPA/AA ratio	0.42 ± 0.03	0.43 ± 0.04	0.42 ± 0.05	0.954
Serum creatinine (mg/dl)	0.78 ± 0.02	0.79 ± 0.02	0.76 ± 0.04	0.577
BNP (pg/dl)	27 ± 2	26 ± 3	30 ± 4	0.575

N-IS = the group of non-ischemic patients, IS = the group of ischemic patients, DM = diabetes mellitus, BP = blood pressure, CVD = cardiovascular disease, EPA = eicosapentaenoic acid, AA = arachidonic acid, BNP = brain natriuretic peptide.

3.2. The baseline therapies for T2DM and CVD (Table 2)

The prevalence of the internal use of insulin, sulfonylurea, metformin, α-GI, thiazolidine-dione, rapid insulin secretagogue, DPP-4 inhibitor, GLP-1 receptor agonist, SGLT-2 inhibitor, and diet alone was 21 (16%), 30 (23%), 54 (42%), 21 (16%), 5 (7%), 7 (5%), 69 (54%), 8 (6%), 3 (2%), and 20 (16%) of the patients, respectively. Further the prevalence of the internal use of statins, anti-platelets, and RAS inhibitors was 60 (47%), 21 (16%), and 51 (40%) (ACE inhibitors vs. ARB = 10 vs. 41) of the patients, respectively.

Table 2
Baseline Therapies for Type 2 DM and CVD.

	All (n = 128)	N-IS (n = 104)	IS (n = 24)	p value (N-IS vs. IS)
Insulin	21 (16%)	14 (13%)	7 (29%)	0.199
Sulfonylurea	30 (23%)	22 (21%)	8 (33%)	0.389
Metformin	54 (42%)	45 (43%)	9 (39%)	0.510
α-Glucosidase inhibitor	21 (16%)	17 (16%)	4 (17%)	0.784
Thiazolidine-dione	5 (4%)	4 (4%)	1 (4%)	0.953
Rapid insulin secretagogue	7 (5%)	6 (6%)	1 (4%)	0.606
DPP-4 inhibitor	69 (54%)	55 (53%)	14 (58%)	0.772
GLP-1 receptor agonist	8 (6%)	7 (7%)	1 (4%)	0.486
SGLT-2 inhibitor	3 (2%)	3 (3%)	0 (0%)	0.083
Diet alone	20 (16%)	18 (17%)	2 (8%)	0.196
Statins	60 (47%)	50 (48%)	10 (42%)	0.574
Anti-platelets	21 (16%)	15 (14%)	6 (25%)	0.210
RAS inhibitors	51 (40%)	40 (39%)	11 (46%)	0.367

N-IS = the group of non-ischemic patients, IS = the group of ischemc patients, DM = diabetes mellitus, CAD = cardiovascular disease, DPP = dipeptidyl peptidase, GLP = glucagon-like peptide, SGLT = sodium-glucose cotransporter, RAS = renin–angiotensin system.